Improving Outcomes of Antipsychotic Treatment in Schizophrenia

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Abbreviations

TIPS: Treatment and Intervention in Psychosis

BeSt InTro: Bergen-Stavanger-Innsbruck-Trondheim

DSM: Diagnostic and Statistical Manual of Mental Disorders

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision

GBD: Global Burden of Disease

DALYs: Disability-Adjusted Life Years

LYL: Years of Life Lost

LAI: Long-Acting Injectable

GNP: Gross National Product

THC: Tetrahydrocannabinol

GWAS: Genome-Wide Associated Studies

D: Dopamine

NMDAR: N-Methyl-D-Aspartate Receptors

GABA: Gamma-Aminobutyric Acid

PCP: Phencyclidine

LSD: Lysergic Acid Diethylamide

5-HT: 5-hydroxytriptamine (Serotonin)

IL: Interleukin

TNF-α: Tumor Necrosis Factor alpha

MHC: Major Histocompatibility Complex

FGA: First-Generation Antipsychotic

SGA: Second-Generation Antipsychotic

EPS: Extrapyramidal Side Effects

A: Adrenergic

H: Histaminic

M: Muscarinic

CBT: Cognitive Behaviour Therapy

PANSS: Positive and Negative Syndrome Scale

GAF: Global Assessment of Functioning

RCT: Randomised Controlled Trial

SST: Social Skills Training

ACT: Assertive Community Treatment

ECT: Electroconvulsive Therapy

DBS: Deep Brain Modulation

TMS: Transcranial Magnetic Stimulation

NICE: National Institute of Clinical Excellence

TRS: Treatment-Resistant Schizophrenia

FES: First-Episode Schizophrenia

BPRS: Brief Psychiatric Rating Scale

PRS: Psychopathology Rating Schedule

CGI: Clinical Global Impression

CGI-S: Clinical Global Impression-Severity

CGI-I: Clinical Global Impression-Improvement

SAPS: Scale for Assessment of Positive Symptoms

SANS: Scale for Assessment of Negative Symptoms

FEP: First Episode Psychosis

SCID: Structured Clinical Interview for DSM-IV Axis I disorders

CDSS: Calgary Depression Scale for Schizophrenia

ITT: Intention-To-Treat

PP: Per Protocol

LCMM: Latent Class Mixed Model

BIC: Bayesian Information Criterion

ANOVA: Analysis of Variance

BASG: Federal Office for Safety in Health Care

ICH-GCP: International Conference on Harmonisation-Good Clinical Practice

APA: American Psychiatric Association

TRRIP: Treatment Response and Resistance in Psychosis

EUFEST: European First Episode Schizophrenia Trial

DDD: Defined Daily Dose

FDA: Food and Drug Administration

PORT: Schizophrenia Patient Outcomes Research Team

PDE: Phosphodiesterase

CBD: Cannabidiol

FAAH: Fatty Acid Amid Hydrolase

AEA: N-arachidonoylethanolamine

TAAR1: Trace Amine Type 1 Receptor

KarXT: Xanomeline-Trospium

Scientific environment

This thesis and the studies included were performed in collaboration with the following research groups and institutions:

TIPS (Treatment and Intervention in Psychosis)-Network for Clinical Research in Psychosis, Clinic for Adult Mental Health, Stavanger University Hospital, Stavanger, Norway.

Bergen Psychosis Research Group (BPRG), NORMENT, Division of Psychiatry, Haukeland University Hospital, Bergen, Norway.

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Abstract in English

Background and Aims

Pharmacological treatment in schizophrenia often yields suboptimal results, regarding both positive and negative symptoms. This thesis aimed to examine outcomes in terms of response and remission and to identify potential predictors of outcomes.

Methods

The first article is a cohort substudy of the Early Treatment and Intervention in Psychosis (TIPS) study, a clinical orientated research project focused on early detection and treatment of psychoses. Our substudy examined the one-year remission rate of patients with first-episode schizophrenia and the pharmacological treatment applied. The final two articles utilised data from BeSt InTro, a randomised controlled trial of three atypical antipsychotics. Response trajectories throughout one-year follow-up were calculated, as were remission rates in various points. Possible predictors for response and remission were explored.

Results

The one-year remission rate in the TIPS study was 32%, and most cases among the non-remitted patients did not follow guidelines for pharmacological treatment. In the randomised antipsychotic trial, 87% of the participants demonstrated a good response after one year. Unemployment, depression and high negative symptom severity at baseline predicted poor response. The one-year remission rate was 29% using consensus remission criteria. Participants who were antipsychotics-naïve and had a low negative symptom load at baseline were more likely to be in remission at one year. Treatment with amisulpride yielded more favourable results compared to treatment with aripiprazole or olanzapine.

Conclusion and consequences

Whilst pharmacological treatment of schizophrenia often has favourable outcomes, areas of improvement exist, especially in treating negative symptoms. Adherence to all steps of the treatment guidelines, more frequent use of clozapine and amisulpride, and

the development of newer pharmacological agents targeting negative symptoms specifically, may enhance these outcomes.

Abstract in Norwegian

Bakgrunn/Formål

Den farmakologiske behandlingen av schizofreni gir langt fra optimale resultater, i forhold til både positive og negative symptomer. Denne avhandlingen hadde som hensikt å undersøke utfall i form av respons og remisjon, i tillegg til å identifisere mulige prediktorer for utfall.

Metoder

Den første artikkelen er en kohort substudie av Tidlig Behandling og Intervensjon i Psykose (TIPS) studien. TIPS er et klinisk orientert forskningsprosjekt som fokuserer på tidlig oppdagelse og behandling av psykoser. Vår substudie undersøker ett års remisjonsrate hos pasienter med første-episode schizofreni, og den farmakologiske behandlingen som deltakerne mottok. De siste to artikler brukte data fra BeSt InTro, en randomisert kontrollert studie av tre atypiske antipsykotika. Responsbaner i løpet av ett års oppfølging, i tillegg til remisjonsraten i forskjellige punkter ble beregnet. Mulige prediktorer for respons og remisjon ble utforsket.

Resultater

Ett års remisjonsrate i TIPS studien var 32%, og retningslinjer for farmakologisk behandling ble ikke fulgt i de fleste tilfellene for de ikke-remitterte pasienter. I den randomiserte antipsykotika studien, hadde 87% av deltakere god respons etter ett år. Arbeidsløshet, depresjon og negative symptomer ved baseline predikerte dårlig respons. Ett års remisjonsrate var 29% ved bruk av konsensus remisjonskriterier. Deltakere som var antipsykotika-naïve og hadde lave negative symptomer ved baseline, hadde høyere sannsynlighet for å være i remisjon etter ett år. Bruk av amisulprid ga bedre resultater sammenlignet med aripiprazol og olanzapin.

Konklusjon og konsekvenser

Utfallet av den farmakologiske behandlingen av schizofreni er bra i mange tilfeller, men det er forbedringsområder, spesielt i behandling av negative symptomer. Bedre etterlevelse av behandlingsretninglinjene, og hyppigere bruk av klozapin og amisulprid, er faktorer som kan forbedre utfallene, i tillegg til utvikling av nyere farmakologiske midler spesielt rettet mot negative symptomer.

List of Publications

Drosos P, Brønnick K, Joa I, Johannessen JO, Johnsen E, Kroken RA, Stain HJ, Hegelstad WTV, Larsen TK. One-Year Outcome and Adherence to Pharmacological Guidelines in First-Episode Schizophrenia: Results From a Consecutive Cohort Study. J Clin Psychopharmacol. 2020 Nov/Dec; 40(6):534-540. doi: 10.1097/JCP.0000000000001303. PMID: 33136922; PMCID: PMC7643791.

Drosos P, Johnsen E, Bartz-Johannessen CA, Larsen TK, Reitan SK, Rettenbacher M, Kroken RA. Trajectories of response in schizophrenia-spectrum disorders: A one-year prospective cohort study of antipsychotic effectiveness. World J Psychiatry. 2022 Mar 19; 12(3):521-532. doi: 10.5498/wjp.v12.i3.521. PMID: 35433321; PMCID: PMC8968498.

Drosos P, Johnsen E, Bartz-Johannessen CA, Larsen TK, Reitan SK, Rettenbacher M, Kroken RA. Remission in schizophrenia spectrum disorders: A randomized trial of amisulpride, aripiprazole and olanzapine. *Under review in Schizophrenia Research*

Contents

1. Introduction

1.1 Schizophrenia

1.1.1 The history of the term "schizophrenia"

While insanity has been a feature throughout human history, it was only at the beginning of the 20th century that Kraepelin described the symptom pattern of dementia praecox[1]. In 1908, Bleuler introduced the term "schizophrenia" for the first time, a word deriving from the Greek words *schizein* ("σχίζειν", to split) and *phren* ("φρέν", originally denoting "diaphragm" but later changing, by metonymy, to "soul, spirit, mind"). Bleuler disagreed with Kraepelin's assertion that dementia was a core symptom of what he had described as dementia praecox:

> "For the sake of further discussion I wish to emphasize that in Kraepelin's dementia praecox it is neither a question of an essential dementia nor of a necessary precociousness. For this reason, and because from the expression *dementia praecox* one cannot form further adjectives nor substantives, I am taking the liberty of employing the word *schizophrenia* for revising the Kraepelinian concept. In my opinion the breaking up or splitting of psychic functioning is an excellent symptom of the whole group"[2].

Instead, Bleuler presented the concept of four core symptoms: abnormal associations, autistic behaviour and thinking, abnormal affect and ambivalence (the four As), and recognised the presence of a spectrum of disorders rather than a one-size-fits-all approach, describing a "group of schizophrenias". The term schizophrenia has since been widely used in the fields of psychiatry and psychology.

1.1.2 The symptom domains and the diagnostic criteria for schizophrenia

Schizophrenia is a severe mental disorder, characterised by a specific syndrome of symptoms. The diagnosis of schizophrenia is based on a clinical assessment, which poses some diagnostic challenges. Early narrative descriptions of the disease were

replaced with codified criteria after the introduction of the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) by the American Psychiatric Association in 1980[3]. This was a significant step in the evolution of the psychiatric classification, contributing to the increased reliability, enhanced standardisation of clinical practice, and improved comparability of follow-up studies[4]. The shift from the subjective, impressionistic diagnostic scheme of DSM-II to the more precise symptom-based diagnosis in DSM-III was largely due to clinicians' improved ability to recognise the characteristic positive symptoms of schizophrenia[5].

In an article identifying textbooks of psychiatry or psychological medicine published from 1900 to 1960, it was found that modern operationalised criteria for schizophrenia reflect symptoms and signs often reported by historical experts, albeit with some changes[4]. Nowadays, the diagnostic criteria for schizophrenia according to DSM-5[6] are frequently used. In Europe, the classification of the World Health Organization is used more commonly, although DSM-5 is used widely in research, and the diagnostic criteria for schizophrenia are those found in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)[7]. ICD-10 has also adopted a criteria-based system, and the two diagnostic systems have become more similar in their recent versions.

Following the development of medical treatment of the symptoms of psychosis and the utilisation of rating scales for symptoms and behaviours, by the mid-1980s separate investigators identified three dimensions or subsyndromes of schizophrenia: positive or psychotic symptoms, the negative symptoms and the disorganisation symptoms[5]. The positive symptoms include hallucinations and delusions, with the most common hallucinations being auditory, followed by visual hallucinations. Tactile (or haptic), olfactory, and gustatory hallucinations are less common, and the least common are visceral or other deep tissue hallucinations (cenesthetic hallucinations). Delusions are a discrete category of thought consisting of ideas inaccessible to normal reason, often defined alternatively as "fixed false beliefs"[5]. There are various types of delusions;

some of these include persecutory, grandiose, religious, somatic, delusions of jealousy, guilt or sin, reference, delusions of being controlled, of mind reading, thought broadcasting, thought insertion and thought withdrawal. The positive symptoms are the most predominant and they are often the reason for which the patient presents to the clinician.

However, most patients also have negative symptoms, which are more stable over time than the positive or disorganisation symptoms. Negative symptoms "represent a loss or diminution of normal functions", whilst the positive symptoms refer to ideas, cognitions and behaviours added to normal mental functions[5]. Negative symptoms include avolition (loss of will or drive), anhedonia (loss of the ability to find or derive pleasure from activities or relationships), blunted affect, passive/apathetic social withdrawal, alogia (decrease in verbal communication), difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking.

The disorganisation symptoms include thought disorders, which refer to the disorganisation of the form of thought, and not content. Vague speech, incomplete sentences, loosening of associations, and confabulation are some forms of these symptoms. In their most severe form, patients may present with mutism, use of neologisms (novel words), echolalia and incoherence. Another category of disorganisation symptoms is the motor symptoms, like subtle repetitive hand movements, or broader, more complex movements involving more parts of the body. Echopraxia refers to the mimicking of the motor behaviours of others. Catatonic symptoms include catatonic excitement (constant purposeless motor activity), negativism (automatic resistance to moving body parts, or direct ambulation), posturing or rigidity, and catatonic stupor.

While more recent descriptions emphasise positive symptoms, earlier conceptualisations saw negative symptoms as core features of the disease because the severity of negative symptoms predicts long-term disability better than the severity of positive or disorganisation symptoms[5]. Schizophrenia usually manifests in early

adulthood, and it is now recognised that a period of attenuated symptoms and impaired functioning typically precedes the first psychotic episode. In recent years, this period in the course of schizophrenia has received much attention, and several interventions have been proposed and implemented for the patients deemed to be at ultra-high-risk of psychosis, in an effort to prevent the development of a first psychotic episode[8]. Further course characteristics after the first episode include multiple episodes, partial or full remission and continuous symptoms[9].

1.2 The impact of schizophrenia

Schizophrenia profoundly affects the individual, family and society in general. It is often associated with recurrent hospitalisations, poor social functioning, low work participation, as well as unemployment[10,11]. Schizophrenia has been called "arguably the worst disease affecting mankind, even AIDS not excepted"[12].

1.2.1 The impact on disability and overall health

In the Global Burden of Disease (GBD) study conducted in 2019, the impact of 369 diseases and injuries in 204 countries and territories was analysed from 1990 to 2019[13]. The results indicated a clear improvement in overall health during that period, when the number for DALYs (Disability-Adjusted Life Years) was adjusted for age. Unfortunately, this positive trend did not apply for schizophrenia – in fact, there has been an increase in the overall impact of this type of mental disorder. The age-adjusted number of DALYs has increased by 11.4% from 1990 to 2019, and the percentage of the overall burden of disease rose from 0.35% to 0.6%.

In 2019, schizophrenia ranked 22nd among all causes of disability for the age group 25-49 years, while it ranked 23rd in the same list for 1990. Moreover, the burden of schizophrenia is likely underestimated, as the GBD methodology does not count

schizophrenia as a direct cause of death, despite the known association between schizophrenia and increased mortality[10].

1.2.2 The impact on mortality

A recent population cohort study of around 7 million individuals in Denmark used the method of estimating years of life lost (LYL). It found a reduced life expectancy for individuals with schizophrenia compared to the general population, with 13.8 and 11.8 life years lost for males and females, respectively[14]. Other studies estimate a reduced life expectancy of approximately 20 years lower than the general population[15].

The question of what causes this excess mortality in schizophrenia has been addressed in many studies. Suicide and accidents account for a part of the mortality causes, but the largest part is due to natural causes of death. A recent literature review on this topic identified five major causes of premature mortality in schizophrenia: adverse effects of medication, suboptimal lifestyle, somatic comorbidity, suboptimal treatment of somatic disorders and accelerated ageing/genetic explanations[16].

The association of antipsychotic treatment with increased or decreased mortality among individuals with schizophrenia remains controversial. However, recent large epidemiological studies, reviews and meta-analyses support the protective effect of antipsychotic agents. An observational cohort study with approximately 30,000 participants from Sweden, found a 50% lower risk of death when using antipsychotics compared with no use[17]. Long-acting injectable (LAI) antipsychotics showed lower mortality than oral agents in the same study. A recent review and meta-analysis of studies spanning from 1957 to 2021 revealed the same protective effect of antipsychotics[18]. The authors suggested long-term maintenance antipsychotic treatment and a more appropriate or earlier use of second-generation LAIs and clozapine to reduce the mortality gap seen in individuals with schizophrenia.

1.2.3 The impact on economy

The burden of schizophrenia can also be quantified in economic costs, both direct and indirect. Direct costs encompass hospitalisation, residential care, day care, pharmaceuticals, laboratory testing and social security payments. Indirect costs, on the other hand, pertain to lost employment costs (working time lost through morbidity and mortality) and familial costs, which may include household expenditure, travel costs, lost earnings, and opportunity cost associated with career time[19].

The World Health Association has estimated that the direct costs of schizophrenia in Western countries range from 1.6% to 2.6% of total health care expenditures, which in turn account for between 7% and 12% of the Gross National Product (GNP)[20]. A systematic review of economic burden studies in schizophrenia, with more than 80% of the studies conducted in high-income countries, estimated that indirect costs accounted for 50-85% of the total costs associated with schizophrenia[21].

In Norway, in 2022, more than 360,000 individuals received disability benefits, constituting roughly 10% of the total population aged 18-67 years[22]. Per June 2017, 321,800 individuals in Norway received disability benefits, with 37.2% of them diagnosed with a psychiatric or behavioural disorder, and 4.4% of the total sample diagnosed with various psychotic disorders, including schizophrenia[23]. The proportion of the psychiatric disorders among the disability benefits recipients increased by 7.7% from 2000 to 2017, concurrent with the increase in young adults (age 18-29) receiving disability benefits, the majority of whom had a psychiatric or behavioural disorder (60-70%, depending on sex). A 12-month national Norwegian study from 2015, which included all individuals receiving specialist treatment for schizophrenia (n=8399), estimated a 12-month prevalence rate of 0.17% for individuals treated for schizophrenia, an employment rate of about 10% and annual societal costs of US$ 890 million[24].

In summary, the heavy burden of schizophrenia across various aspects of human life is unmistakable. There is a clear discrepancy between the relatively low prevalence of this disease and its profound impact on the individual and society as a whole.

1.3 The epidemiology of schizophrenia

Epidemiology is the study of distribution and determinants of disease[25]. For schizophrenia, these determinants encompass both genetic and environmental risk factors. Despite significant advances in our understanding of the causation of schizophrenia over recent decades, the specific exposures involved and their precise role in causing schizophrenia remain unclear. Generally, the distribution of a disease is expressed by "incidence" (new cases) and "prevalence" (total number of cases: existing + new cases). This is illustrated in Figure 1[26].

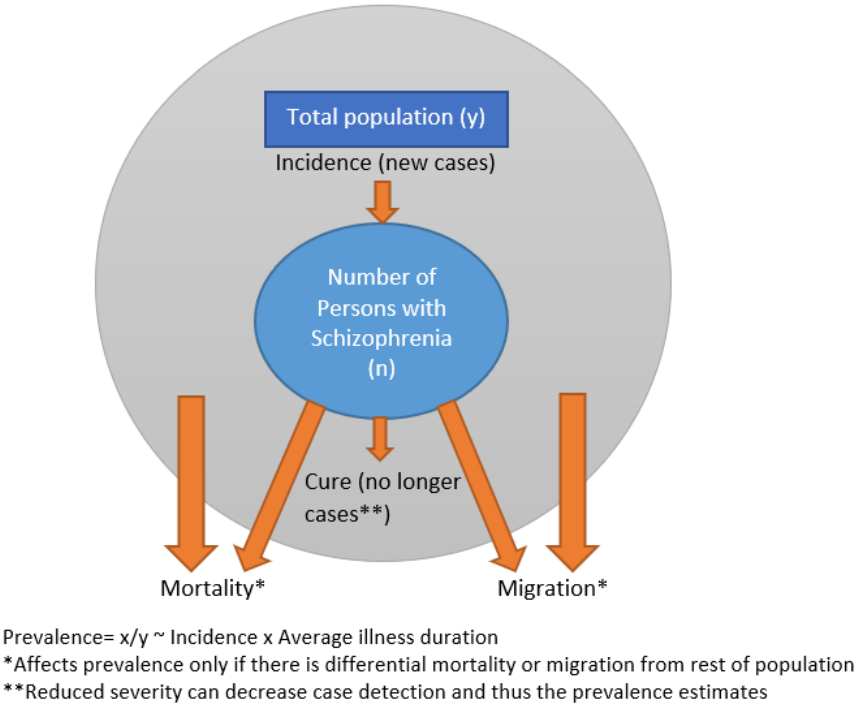

Figure 1. **Relation between incidence and prevalence in a given population.** *Modified from figure published in Schizophrenia Research, Jul 2008; 102 (1-3):1-18, Tandon R, Keshavan MS, Nasrallah HA; Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. Copyright Elsevier.*

1.3.1 The incidence of schizophrenia

"Incidence" refers to the emergence of new disease cases over a specified period. Generally, the incidence rate is variable among studies, and the estimates range from 4-72 per 100.000 person-years (median 30; interquartile range 13–41)[27]. In a systematic review of the incidence of schizophrenia[28], the authors found considerable variation between sites (persons, median n = 15.2 per 100,000; 10%–90% quantiles = 7.7–43.0). The study further established that (a) males were more prone to develop schizophrenia

than females (median male: female risk ratio = 1.4); (b) immigrants were more likely to develop schizophrenia than native-born individuals (median risk ratio = 4.6); and (c) individuals in urban areas were more likely to develop schizophrenia than those in mixed urban/rural areas. These findings dispute previous notions of consistent schizophrenia rates worldwide. A Finnish epidemiological study[29] indicated a significant decline in the incidence of schizophrenia in Finland in the birth cohorts from 1956 to 1989, with potential explanations including: improved treatment of psychosis in the prodromal stage, which may shift the diagnoses towards later ages; changes in diagnostic practices over time, which may have affected the distribution between different diagnoses; and enhanced monitoring and development of pre- and postnatal care, as complications in these situations have been associated with increased risk of schizophrenia[30]. During the same period of the study, the cumulative incidence of catatonic schizophrenia plummeted by over 90%, a trend thought to be associated with the eradication of polio. Polio vaccination was introduced in Finland in 1957, and at that time all children born in 1940 or later were vaccinated. The authors concluded that this association may point towards a possible causal link between prenatal or infancy exposure to polio and later development of catatonic schizophrenia. This association underscores the role of environmental factors in the development of schizophrenia. It further highlights the importance of robust public health, such as the prevention of viral infections, in reducing the incidence of schizophrenia.

1.3.2 The prevalence of schizophrenia

"Prevalence" denotes the proportion of a population with a specific disease or condition either at a particular time (point or period prevalence) or any time during their life (lifetime prevalence)[26]. While schizophrenia prevalence varies across studies, a global lifetime prevalence rate of around 1% is widely accepted, as reflected in DSM-IV and in several textbooks. However, a systematic review encompassing 188 studies with a total of 1,721 estimates drawn from 46 countries, found a median point prevalence of

4.6 per 1,000 persons and a lifetime prevalence of 4.0 per 1,000 persons[31]. The authors noted no significant difference between male and female nor between urban, rural and mixed sites, but did observe higher prevalence for schizophrenia rates among immigrants, and "emerging" and "developed" sites compared to "least developed" countries in terms of economic status. The authors discussed these lifetime prevalence figures against those reported in DSM-IV and psychiatry textbooks, considering the impact of factors influencing prevalence, such as recovery from schizophrenia, suicide, and other forms of early mortality. It seems that there may still be some confusion around the concept of prevalence in schizophrenia, particularly whether patients who have recovered, albeit with residual disability, should be counted as "active" cases.

1.4 The pathogenesis of schizophrenia

Schizophrenia is a complex and heterogeneous disease, with its pathogenesis remaining largely unclear. The diseases's origin seems to lie in a delicate interplay between environmental and genetic factors, with evidence suggesting that the pathogenesis of schizophrenia begins early in neurodevelopment.

1.4.1 Environmental factors

There are several studies that indicate the influence of early neurodevelopment factors during pregnancy including maternal stress, maternal infections, nutritional deficiencies, intrauterine growth retardation, and pregnancy and obstetric complications[32]. Meta-analyses on this topic[30] have identified three groups of obstetric complications, which are associated with higher risk for schizophrenia: 1) pregnancy complications such as bleeding, diabetes, rhesus incompatibility, preeclampsia; 2) abnormal fetal growth and development, indicated by low birthweight, congenital malformations, reduced head circumference, and 3) complications of delivery such as

uterine atony, asphyxia, and emergency Cesarean section. However, the effect sizes for these relationships are relatively small (odds ratios less than 2) and the authors underline that this phenomenon might reflect the search for uncommon risk factors for a rare disease.

Additional associated environmental factors encompass socioeconomic parameters, childhood adversity, and first- and second-generation immigrant background. The role of childhood trauma has been addressed in several studies, although the findings are not specific to schizophrenia[33]. In a meta-analysis of studies examining the association between childhood adversity and trauma and psychosis outcome, the authors concluded that childhood adversity is strongly associated with increased risk for psychosis (odds ratios 2.75-2.99)[34]. Conditions such as birth in late winter or early spring, being born and raised in an urban environment, and having relatively old fathers are further associated with higher rates of schizophrenia. Substance use, particularly the use of cannabis compounds with high tetrahydrocannabinol (THC) content, has been implicated in the development of schizophrenia. Other proposed factors include head injury, epilepsy, autoimmune diseases and severe infections. Despite the robustness of these associations, with recent meta-analyses yielding odds ratios between 1.5 and 3.0, caution is necessary when interpreting these results. This is due to an inherent limitation in observational epidemiology that fails to distinguish true causation from association, owing to confounding, pleiotropy and reverse causation[32].

1.4.2 Genetic factors

Heritability refers to the proportion of variance in liability for an illness in the general population that is attributable to genetic influences — both independently and through interactions with environmental factors[26]. Twin studies and other research have indicated a substantial genetic component to schizophrenia, with heritability estimated to be around 80%. Studies with dizygotic twins, who share 50% of their genetic

material, have shown that if one twin has schizophrenia the risk for the other twin is 10-15% (similar to this in siblings who also share 50% of their genes). For monozygotic twins, this risk increases to approximately 50%[26,35].

High heritability underscores the significant role of inherited genetic variants in the etiology of schizophrenia. Genome-wide associated studies (GWAS) have found that common alleles explain between one-third and one-half of the genetic variance in liability[36]. In a recent study, the authors reported findings from a new GWAS and, through a meta-analysis with existing data, they identified 50 novel associated loci and 145 loci in total[36]. Another GWAS from the Schizophrenia Working Group of the Psychiatric Genomics Consortium, with around 37,000 cases with schizophrenia and 113,000 controls, identified 128 independent associations spanning 108 loci, 83 of which had not been previously reported[37]. Associations with genes expressed in the brain and involved in glutamatergic neurotransmission align with known potential psychopathological pathways. However, novel findings concerning genes expressed in peripheral tissues playing an important role in immunity support the hypothesised link between the immune system and schizophrenia[37]. In the most recent and largest GWAS in schizophrenia to date, published in 2022, a significantly increased number of associated loci was identified[38]. The authors concluded that neurons seem to be the most important site of pathology in schizophrenia, and they suggested high pathophysiological importance of pre- and post-synaptic locations, and functions related to synaptic organisation, differentiation and transmission. These advances in understanding the genetic profile of schizophrenia may bring us closer to understanding the pathophysiology of this disorder and contribute to the development of new therapeutic agents with mechanisms of action different from traditional antipsychotic drugs.

In summary, there is considerable evidence pointing to the involvement of multiple genetic and environmental factors, both biological and psychosocial, in the pathogenesis of schizophrenia. Genetic factors, as well as early developmental

exposures, may increase susceptibility to later risk factors for schizophrenia. There is a need for larger studies that combine genomics with epidemiology, which will help elucidate potential environmental causes and ultimately pave the way to primary prevention[32].

1.5 The pathophysiology of schizophrenia

1.5.1 The contribution of brain imaging and neuropathological studies

Numerous brain imaging and neuropathological studies have endeavoured to link schizophrenia to altered structure or functions of certain brain regions and circuits[39]. The involvement of the prefrontal cortex, particularly concerning specific cognitive deficits, and subtle reductions in grey matter and abnormalities in the white matter in many brain regions and circuits such as the caudate nucleus and thalamus, have been associated with schizophrenia. However, the intricacies of brain networks are beyond the scope of this thesis and will not be covered in any further detail.

1.5.2 The dopamine hypotheses

At the cellular level, there is substantial evidence implicating dysfunction in dopaminergic neurotransmission in the manifestation of positive psychotic symptoms, like hallucinations and delusions. The initial version of the dopamine hypothesis of schizophrenia emerged in the 1960s, following the introduction of the first antipsychotic, chlorpromazine, a decade earlier. This drug proved particularly effective in treating positive symptoms in patients with schizophrenia[40,41], and subsequent research revealed an increase in dopamine metabolites when these drugs were administered to animals[42]. The development of newer antipsychotics largely drew from

the dopamine hypothesis, which posits that increased mesolimbic dopamine activity plays a significant role and can be normalised by the use of dopamine antagonists, especially dopamine-2 (D2) receptor antagonists.

In a landmark article by Davis et al., the authors introduced a second version of the dopamine hypothesis, which they called "a modified dopamine hypothesis of schizophrenia"[43]. The main change from the first version of the dopamine hypothesis was the addition of regional specificity, suggesting that the effects of the dopamine abnormalities could vary by brain region. More specifically, this hypothesis suggested frontal hypodopaminergia and subcortical hyperdopaminergia. The negative symptoms in schizophrenia were hypothesised to be a result of frontal hypodopaminergia, while the positive symptoms might stem from striatal hyperdopaminergia[44]. This hypothesis is summarised in Figure 2.

In 2009, Howes and Kapur proposed a third version of the dopamine hypothesis of schizophrenia[44]. This incorporated the hypothesis that multiple "hits" interact to result in dopamine dysregulation, primarily at the presynaptic dopaminergic control level. It also proposed that dopamine dysregulation is connected to "psychosis" rather than schizophrenia. This version of the hypothesis suggests that changes in multiple transmitter/neural systems underlie the negative symptoms and cognitive dysfunction seen in schizophrenia, which often precede the onset of the disorder. The authors left open the question of whether this hypothesis applies specifically to the psychosis of schizophrenia or extends to psychosis in other disorders.

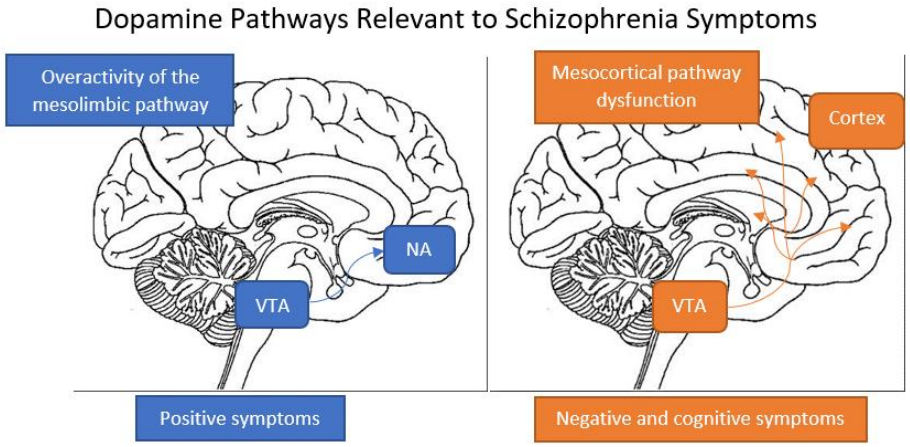

Figure 2. **A summary of a modified dopamine hypothesis of schizophrenia showing the variation of the dopamine abnormalities by brain region.**

Modified from figure published online by the Psychopharmacology Institute (Psychopharmacology: antipsychotics & The Dopamine Hypothesis)[45].

1.5.3 The glutamate hypothesis

The glutamate hypothesis of psychosis suggests that hypofunctional N-methyl-D-aspartate receptors (NMDAR) on gamma-aminobutyric acid (GABA) interneurons in the prefrontal cortex (potentially due to abnormal neurodevelopment) cause overactive glutamate signalling. This overstimulation of the mesolimbic dopamine pathway may cause auditory hallucinations and paranoid delusions[46].

Recent findings have pointed towards the critical role of glutamatergic dysfunction, particularly in cognitive impairment[47]. Historically, glutamatergic theories were developed following the synthesis of the dissociative anaesthetics phencyclidine (PCP) and ketamine in the late 1950s[48]. Shortly thereafter their psychotogenic potential in humans was demonstrated[49], the PCP receptor was discovered[50], and finally these

compounds were found to function by blocking the NMDAR channel[51]. Notably, PCP and ketamine induced negative symptoms and cognitive dysfunction similar to that observed in schizophrenia, suggesting that this model could be particularly relevant to persistent, poor-outcome forms of schizophrenia. This finding represents a promising treatment target for schizophrenia, especially given that negative symptoms and cognitive impairment often do not respond satisfactorily to traditional antipsychotics.

1.5.4 The role of serotonin

In addition to glutamatergic dysfunction, other neurotransmitters such as serotonin, acetylcholine and GABA have also been implicated in the pathophysiology of schizophrenia[52]. The serotonin hypothesis is based on the observations of the interactions between the hallucinogenic drug lysergic acid diethylamide (LSD) and serotonin (5-hydroxytryptamine [5-HT]). Moreover, the antipsychotic effects of serotonin-dopamine antagonists, such as risperidone and clozapine, further support a potential role of these two neurotransmitter systems in the pathophysiology of schizophrenia.

1.5.5 The role of acetylcholine

As for acetylcholine, there is evidence suggesting that the cholinergic modulation affects both positive and negative symptoms in schizophrenia[53]. In addition, there is neuroendocrine and polysomnographic data suggesting an increased muscarinic cholinergic activity in schizophrenia. More observations supporting the further evaluation of this theory include the fact that clozapine, which boasts a unique therapeutic profile, shows its highest affinity for the muscarinic receptor, the use of anticholinergic drugs to treat extrapyramidal side effects and the fact that many antipsychotic agents also have anticholinergic activity.

1.5.6 The role of GABA

Lastly, GABA, the primary inhibitory neurotransmitter in the central nervous system, has been implicated in schizophrenia pathophysiology. Alterations in the GABA system have been reported in clinical and basic neuroscience studies and animal models[54]. GABAergic compounds have been found to improve core symptoms of schizophrenia suggesting their potential utility in conjunction with antipsychotics[55].

1.5.7 The role of the immune system

Indeed, the role of the immune system in the pathophysiology of schizophrenia has drawn increased attention in the recent years. The association between psychosis and various infectious or autoimmune processes has been demonstrated through clinical, genetic and epidemiological studies[56,57]. Prenatal maternal infection with pathogens such as influenza, herpes simplex virus type 2, cytomegalovirus, and Toxoplasma gondii, as along with nonspecific viral and bacterial infections and increased maternal C-reactive protein during pregnancy, have all been associated with structural and functional brain abnormalities relevant to schizophrenia, and subsequently the development of schizophrenia[58,59]. There is also an association between subclinical psychotic experiences in adolescents[60] and schizophrenia in adults[61] with autoimmune conditions in childhood.

A review of studies on the cytokine profile of non-medicated patients with early psychosis found a significant increase in pro-inflammatory cytokines like interleukin 6 (IL-6), IL-1β, and tumor necrosis factor alpha (TNF-α), strengthening the evidence of pro-inflammatory immune dysregulation in schizophrenia[62]. Oxidative stress has also been studied, as significant oxidative damage and a decrease in antioxidants such as glutathione have been observed in the periphery of individuals with schizophrenia[63].

Findings from GWAS report significant associations between schizophrenia and markers near the major histocompatibility complex (MHC) region on chromosome 6, a region involving many immune-related genes[64,65]. A major GWAS study from 2014[37], which identified 108 genetic loci associated with schizophrenia, found many of them represent genes involved in adaptive immunity, in addition to MHC.

These findings have important therapeutic implications and there is growing research into the use of anti-inflammatory drugs in schizophrenia[66,67], including neurosteroids, statins, N-acetyl cysteine, glitazones and melatonin[68]. A systematic review and meta-analysis of the efficacy of these agents found an effect for psychotic disorders, however a meta-regression showed decreasing effects with increasing sample sizes, suggesting that the treatment effect might be overestimated due to the preponderance of small studies[68].

1.5.8 Conclusion

In conclusion, schizophrenia is a complex and heterogeneous disorder, and the dysfunctions cannot be explained by a single neurotransmitter abnormality. Although the core pathophysiology of schizophrenia might primarily involve dopaminergic anomalies, other systems involving glutamate, serotonin, acetylcholine, and GABA might play a role in the development of negative and cognitive symptoms. It is possible that there is an interaction between neurotransmitter systems that lead to complex mechanisms involved in the pathophysiology of schizophrenia. Leading experts in the schizophrenia field support the idea that a drug targeting multiple neurotransmitter systems or a combination of therapeutic agents, including immune-modulating drugs, might be the most successful therapeutic strategy in the treatment of schizophrenia[40].

1.6 Pharmacological treatment of schizophrenia

Efficient pharmacological treatment of schizophrenia did not emerge until the 1950s with the introduction of the first effective antipsychotic drug chlorpromazine. When Emil Kraepelin first described the concept of schizophrenia at the beginning of the previous century, he claimed that "the treatment of dementia praecox offers few points of intervention"[1]. Indeed, the treatment of schizophrenia during the first five decades after the disorder's conceptualisation largely consisted of long-stay admissions in psychiatric hospitals, often having the form of asylums, with the clinicians hoping that a spontaneous remission of psychosis would occur.

1.6.1 Biological treatment of schizophrenia

Nonetheless, clinicians of that era made numerous attempts to treat the symptoms of the disorder. The history of biological therapies in schizophrenia can be divided in two periods, with the discovery of the chlorpromazine marking the dividing line. Several treatments were administered to patients with psychosis during the first period, including sedating agents like bromides and barbiturates, hydrotherapy and wet sheet packs, seizure-inducing drugs like camphor and pentylenetetrazol, and insulin coma therapy[5,69]. Regrettably, these therapies were never exposed to adequate research trials, as most were abandoned after the introduction of the first effective antipsychotic drugs[5]. Another intervention used at that time was prefrontal leucotomy[70], now considered highly unethical.

1.6.2 The emergence of chlorpromazine and the first antipsychotic drugs

Chlorpromazine was fortuitously discovered in the early 1950s by the French surgeon Laborit, who observed that patients administered this drug prior to surgery were remarkably less anxious about the procedure[5]. In 1952, Laborit persuaded Delay and

Deniker to administer chlorpromazine to psychotic and excited patients. The results were astounding regarding the efficacy of chlorpromazine in reducing hallucinations, delusions, and excitement[41], although side effects, mostly in the motoric domain, were also noted. The use of chlorpromazine rapidly spread through the psychiatric hospitals in Paris, and eventually, the rest of the world. Following the introduction of chlorpromazine, other antipsychotic drugs were developed that showed similar effectiveness: thioridazine, fluphenazine, haloperidol, thiothixene[5]. Three of these drugs (chlorpromazine, fluphenazine, and haloperidol) are included in the World Health Organization's list of Essential Medications[71].

1.6.3 An overview of the current antipsychotic drugs

Due to the incomplete understanding of the etiology and pathophysiology of schizophrenia, the current antipsychotic drugs primarily aim to alleviate the symptoms of the disorder. The goal of the treatment is to reduce patient suffering and improve cognitive and social functioning. Antipsychotic drugs are particularly effective in relieving positive symptoms such as hallucinations, delusions and thought disorder, as well as in preventing relapse. Over 60 different types of these drugs have been developed and they are classified into first- and second-generation agents. Most of them are dopamine receptor antagonists, and many have affinity for other neurotransmitter targets, particularly serotonin receptors. Antipsychotic drugs are used to treat psychosis in several disorders, in addition to schizophrenia, such as psychotic depression, mania and paranoid psychosis.

1.6.4 The first-generation antipsychotics

First-generation antipsychotics (FGAs) are also referred to as typical or conventional antipsychotics. What makes an antipsychotic conventional is the potent ability to block

D2 receptors. The therapeutic properties of these drugs stem from D2 blockade, particularly in the mesolimbic dopamine pathway, which reduces the dopamine hyperactivity associated with positive psychotic symptoms[44]. Unfortunately, it is impossible to selectively block the D2 receptors in the mesolimbic pathway, as these antipsychotics indiscriminately block all D2 receptors in the brain[72]. This leads to side effects which moderate the clinical effect of the antipsychotic drugs: motor effects (blocking D2 receptors in the nigrostriatal pathway), hyperprolactinemia (blocking D2 receptors in the tuberoinfundibular pathway), anhedonia (blocking D2 receptors in the reward system component in the mesolimbic pathway), or even exacerbation of negative symptoms of the disease (blocking D2 receptors in the prefrontal cortex)[73]. The role of dopamine-1 (D1) receptors in the prefrontal cortex has also been studied in animal models and it appears that deficient dopamine function within dorsolateral prefrontal cortex leads to cognitive deficits such as working memory, and that treatments augmenting D1 receptor stimulation can improve cognitive function in schizophrenia[74]. Some antipsychotics act on multiple receptors (e.g., antagonism at muscarinic and $5HT_2A$ receptors), which can, in various degree, reduce the side effects caused by blocking D2 receptors.

1.6.5 Clozapine

As previously stated, one of the main drawbacks of the FGAs is their strong propensity to cause extrapyramidal side effects (EPS), such as Parkinsonism, dystonias, akathisia, as well as the longer-term problem of tardive dyskinesia. A new era in the pharmacological treatment of schizophrenia began with the introduction of clozapine, considered as the archetype of the atypical or second-generation antipsychotics (SGAs). Clozapine was discovered in 1958 and first studied during the 1960s[5]. The atypicality of clozapine refers to the "atypical" clinical effect of being highly efficacious with very low propensity for EPS. Clozapine is characterised by a high ratio of $5HT_2$:D2 receptor occupancy. It was found to be especially effective in treatment-

resistant patients, however, in 1976, it was associated with a considerable risk of agranulocytosis. This side effect, which is potentially fatal and occured in around 1% of the patients, led to the withdrawal of clozapine from the market for several years until a study in 1988 demonstrated its clinical superiority[75]. Clozapine was then reintroduced for treatment-resistant patients, accompanied by stringent haematological monitoring controls. It now holds a central place in all major guidelines for the treatment of schizophrenia as the third-line choice when two previous trials with first-line antipsychotics have not showed sufficient efficacy and/or have caused unacceptable side effects[76,77]. Clozapine has also showed stronger ability to reduce negative symptoms in schizophrenia[78], it has demonstrated anti-suicidal properties[79,80], and has been found to reduce aggression and violence in patients with schizophrenia[81].

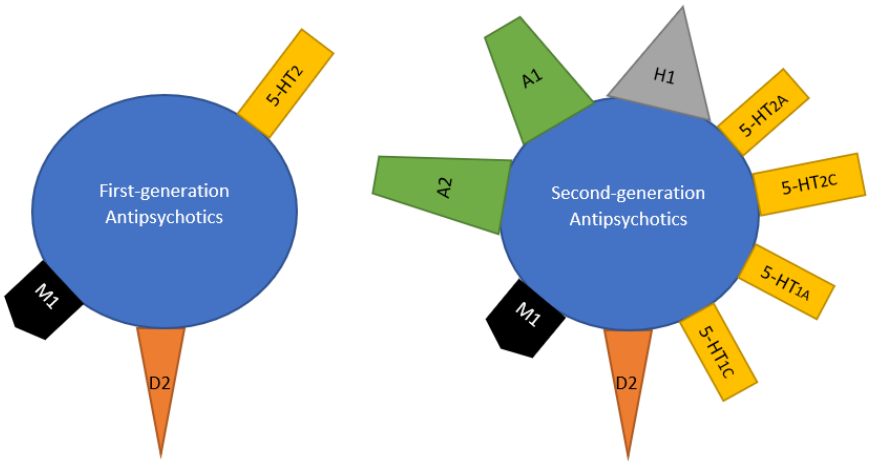

Figure 3. **The main receptor-binding profiles of the first-generation and the second-generation antipsychotics**

Figure 3. **The neurotransmitters involved in the mechanism of action of the first-generation and the second-generation antipsychotics.**

D: Dopamine, 5-HT: 5-hydroxytriptamine (Serotonin), A: Adrenergic, H: Histaminic, M: Muscarinic

1.6.6 The second-generation antipsychotics

Following the re-introduction of clozapine, a number of SGAs were developed: risperidone in 1994, olanzapine in 1996, quetiapine in 1997, ziprasidone in 2001 etc.[5] The group of atypical antipsychotics consists of a variety of drugs with differences in their receptor-binding profiles, side effects, and possibly some differences in efficacy against particular symptoms in different patients[78]. These are effective in doses that usually do not result in severe EPS, as they are found to block serotonin receptors and/or subcortical dopamine receptors to a greater extent than striatal D2 receptors. However, SGAs are also associated with Parkinsonism and other neurological side effects, as all currently available antipsychotics are believed to work mainly via D2 receptor blockade[82]. Additionally, most SGAs are associated with other adverse effects with potential serious consequences, such as metabolic side effects (weight gain, diabetes, dyslipidemia) and an increased risk of cardiovascular complications. It can be stated that what makes an antipsychotic "atypical" from a clinical perspective is the clinical properties that distinguish them from FGAs, namely "low EPS" and "good for negative symptoms"[72]. From a pharmacological point of view, this class of antipsychotics may be defined in at least four ways: as "serotonin dopamine antagonists", as "D2 antagonists with rapid dissociation", as "D2 partial agonists" and as "serotonin partial agonists"[72]. The relationship between mechanism of action, therapeutic effect, and side effects in SGAs are summarized in Figure 4.

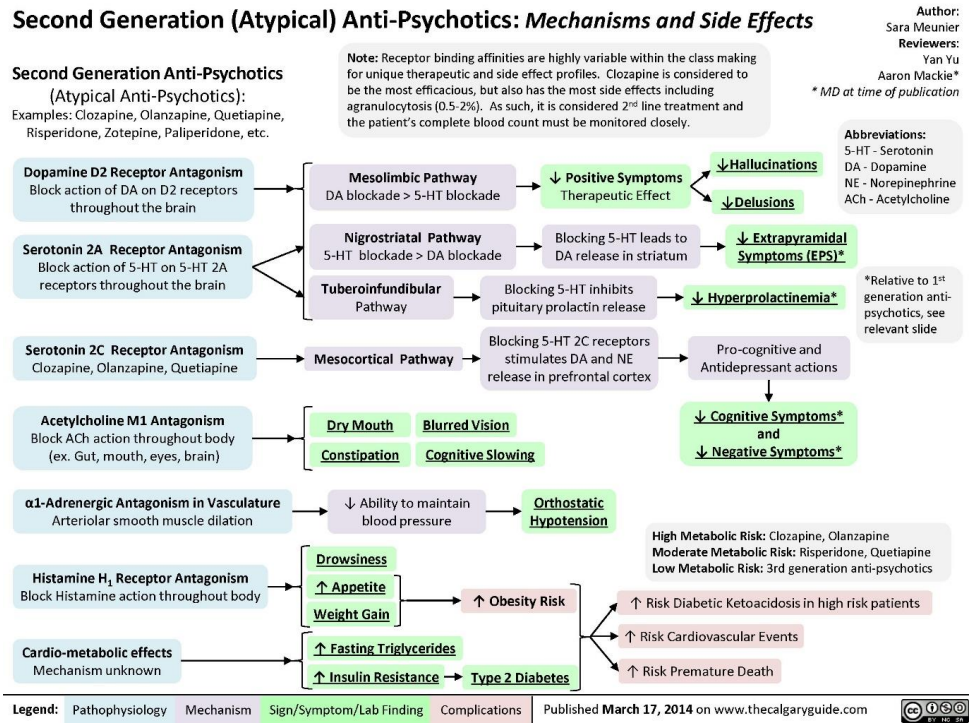

Figure 4. **The relationship between mechanism of action, therapeutic effect and side effects in second-generation antipsychotics.**

Reproduced with permission from The Calgary Guide to Understanding Disease, a collaborative student/faculty project of the University of Calgary. For this, and other materials which illuminate the connection between pathophysiology and clinical manifestation of disease, visit www.thecalgaryguide.com.[83]

1.6.7 Amisulpride

Amisulpride, an atypical antipsychotic, merits individual mention. It demonstrates a high affinity for dopamine receptors, while showing little to no affinity for other receptors in the brain, such as serotonin 2A or 1A receptors[72]. This suggests that amisulpride acts as a dopamine partial agonist at D2 receptors. These unique properties

potentially account for its low propensity for EPS and its capacity to alleviate negative symptoms, particularly at low doses. In terms of side effects, amisulpride generally has a favourable profile, though hyperprolactinemia is commonly reported.

1.6.8 The third-generation antipsychotics

In recent years, a new group of antipsychotics has been developed. Some refer to these as third-generation antipsychotics, but it remains more accurate to classify them as atypical antipsychotics. This group, which includes aripiprazole, brexpiprazole and cariprazine[72], differs from other SGAs in that they are not D2 receptor antagonists, but rather D2 partial agonists. Aripiprazole, the first drug developed in this group, acts as partial antagonist in areas with high extracellular concentrations of dopamine (for example in mesolimbic pathways), resulting in clinical benefits. Conversely, in areas with low extracellular dopamine concentration (e.g., in dopamine circuits in the prefrontal cortex involved in working memory), aripiprazole partially activates dopamine receptors. Aripiprazole is therefore termed a "dopamine stabiliser". An example is the effect of dopamine partial agonists on prolactin levels. Unwanted D2 receptor blockade in the tuberoinfundibular dopamine pathway by conventional antipsychotics causes elevation of plasma prolactin levels, a condition known as hyperprolactinemia. This can lead to conditions like galactorrhea, amenorrhea, more rapid demineralisation of bones, sexual dysfunction and weight gain[72]. Hence, aripiprazole, with its partial dopamine agonist function, can counteract hyperprolactinemia caused by other antipsychotic drugs. Brexpiprazole and cariprazine share a similar mechanism of action with aripiprazole.

The glutamatergic and cholinergic systems are believed to play a role in the symptomatology of schizophrenia, particularly in relation to the negative and cognitive symptoms. While several drugs with various mechanisms of action are under

investigation, there has yet to be any effective treatment involving these systems approved[84,85].

To summarise, antipsychotic drugs have long been pivotal in the treatment of schizophrenia. Even though their efficacy in managing positive and, especially, negative symptoms of schizophrenia is variable and far from optimal, these drugs have contributed significantly to the improved functioning of patients with schizophrenia, as well as to shorter periods of inpatient treatment, and, finally, to the implementation of other types of treatment for schizophrenia.

1.7 Non-pharmacological treatment of schizophrenia

Pharmacotherapy is typically not sufficient on its own to treat patients with schizophrenia, particularly when it comes to addressing negative symptoms, cognitive and social functioning, and overall quality of life. Many patients continue to experience residual positive symptoms and relapses, and adherence to prescribed antipsychotic medication remains a significant challenge contributing to negative outcomes. As such, a comprehensive, multi-dimensional treatment for schizophrenia, encompassing various psychosocial interventions alongside antipsychotic medication, is necessary[40].

1.7.1 Psychosocial interventions

Psychoeducational interventions, particularly those including family members like the single- or multi-family psychoeducation groups, can alleviate high levels of expressed emotion among relatives, and decrease rates of relapse and rehospitalisation[86]. The objective of these interventions is to provide patients and their family members with

detailed information about the disorder and impart strategies to cope with the illness effectively.

Cognitive Behaviour Therapy (CBT) seeks to help patients with schizophrenia to evaluate their psychotic symptoms rationally and to respond to them in a less distressing manner[87]. The ultimate goal is to alleviate the burden of symptoms and to prevent relapses. CBT is now recommended as standard care for people with schizophrenia[76]. Nevertheless, meta-analyses have shown only modest effect sizes for all the symptom classes considered[88] leading some to suggest that after 30 years of trials, CBT is unlikely to ever have more than a minor effect on core psychotic symptoms like hallucinations and delusions[85].

According to a Cochrane review of individual psychodynamic psychotherapy and/or psychoanalysis for people with schizophrenia or other severe mental illness, the authors found no evidence of any positive effect of psychodynamic psychotherapy for hospitalised people with schizophrenia[89]. Conversely, a prospective Danish study comparing individual psychodynamic psychotherapy for psychosis with standard treatment in patients with first-episode schizophrenia spectrum disorders, found significant improvements in both the Positive and Negative Syndrome Scale (PANSS)[90] and the Global Assessment of Functioning (GAF)[91] scores at two-year follow-up[92]. The Norwegian guidelines for the treatment of psychosis emphasise the importance of a psychodynamic understanding for establishing a well-functioning relationship with the patient and the family[93]. Therapeutic conversations can assist the patient in managing stress, relating to psychotic symptoms more effectively, and preventing secondary complications related to e.g., the family, friends, school, work etc. There are generally few randomised controlled trials (RCT) on psychoanalysis or psychodynamic psychotherapy for psychosis, and research is hard to perform due to the complex nature of these interventions.

Cognitive remediation approaches focus on compensation strategies to organise information, use of tools like reminders and prompts, and techniques used to improve

executive function and social cognition. A recent meta-analysis involving 130 studies and 8,851 participants, found cognitive remediation effective in improving cognition and functioning, especially when integrated with psychosocial rehabilitation[94].

Social Skills Training (SST) aims to improve everyday living skills in patients with schizophrenia and focuses on aspects such as self-care, basic conversation, vocational skills and recreation. A meta-analysis including 27 RCTs and 1,437 participants with psychotic disorders indicated an effect of SST for negative symptoms similar to that commonly reported for CBT for positive symptoms[95]. SST, unlike CBT, is not routinely included in treatment guidelines for psychological intervention in schizophrenia.

Assertive Community Treatment (ACT) is an outreach strategy that provides training in community living for psychiatric patients[96]. Key elements of ACT include working in teams to achieve lower patient-to-staff ratios, multidisciplinary teams, providing home visits that promote both health and social care, and being assertive about the provision of treatment and adherence to medication[97]. An analysis of data from selected individual published studies on ACT, as along with reviews from the Cochrane library and other study groups, suggests potential benefits of using ACT, particularly in reducing hospitalisation, but also probably when rate of remission is used as an outcome measure[98].

Supported employment incorporates elements such as individually tailored job placement, rapid job searches, focus on client preferences in services and job searches, individualised and long-term support, close collaboration with the treatment team and personalised counselling on social security and other benefits[40]. A meta-analysis found that supported employment yielded better competitive employment outcomes for individuals with severe mental illness compared to alternative vocational programs[99].

Other non-pharmacological interventions for schizophrenia include crisis intervention[100] and arts therapy, with the latter including music therapy, drama

therapy[101] and dance therapy[102]. Studies have highlighted the beneficial effect of music therapy, particularly for negative symptoms of schizophrenia[103]. Moreover, exercise therapy can improve symptoms, enhance cognitive function and quality of life in patients with schizophrenia, as well as their physical health[104,105].

1.7.2 Biological, non-pharmacological types of treatment

Beyond the realm of psychosocial interventions in the treatment for schizophrenia, there are other biological, non-pharmacological types of treatment. Electroconvulsive therapy (ECT) was once used more widely for the treatment of schizophrenia, but it has seen decreased usage following the emergence of antipsychotic drugs. In a review of the evidence for the use of ECT in schizophrenia, the authors state that there is evidence for the beneficial effect of ECT for patients who are treatment resistant and those not responding to clozapine. Other indications of ECT in schizophrenia include the management of catatonia, suicidal behaviour, and severe agitation, though cognitive deficits associated with ECT remain a concern. Despite this, ECT is underutilised in most developed countries in the treatment of schizophrenia and well-designed large-scale studies are needed to evaluate the short-term and long-term efficacy and side effects of ECT in patients with schizophrenia. Notably, ECT demonstrates a potent effect in the treatment of depression with psychosis[106].

Deep brain modulation (DBS) operates by modulating the striatum and eligible patients with schizophrenia are selected based on symptoms severity, chronicity (persistence of symptoms for at least 12 weeks despite adequate treatment with antipsychotics), functional impairment evaluated through validated scales, clinical interview and history, as well as treatment refractoriness (at least two adequate antipsychotic trials for a minimum of 6 weeks each with at least 80% adherence and failure to respond to an adequate trial of clozapine, or inability to tolerate clozapine at the recommended

dose or duration)[107]. Some results from studies are encouraging, but there is a need for the development of neurophysiological biomarkers that can assist DBS targeting[107].

Transcranial magnetic stimulation (TMS) is a non-invasive neuromodulation technique, generally affecting superficial cortical regions. Repetitive TMS (rTMS) is the most frequently used modality. Other types include deep TMS, where the magnetic field penetrates deeper subcortical regions of the brain, and Theta Burst Stimulation (TBS), in which the frequency of stimulation mimics endogenous theta waves. A systematic review and meta-analysis of the efficacy of TMS for negative symptoms in schizophrenia[108] concluded that TMS is efficacious in the treatment of negative symptoms of schizophrenia, though optimal treatment parameters are yet to be established.

1.7.3 Conclusion

In conclusion, there is a variety of studies examining non-pharmacological approaches in the treatment of schizophrenia, taking into account effect sizes and methodological issues. There is no doubt that these types of treatment provide an important supplementary tool and can help improve outcomes where antipsychotics alone do not achieve sufficient efficacy. These outcomes include negative symptoms of schizophrenia, cognitive dysfunction, family involvement, adherence to treatment and vocational skills.

1.8 Guidelines for the treatment of schizophrenia

Clinical practice guidelines are “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances”[109]. These guidelines are founded on research evidence, experience-based knowledge and consumer-based participation and experience, facilitating its

translation into knowledge-based clinical practice. Both international and Norwegian guidelines for the treatment of schizophrenia, agree on a multidimensional approach, where the pharmacological treatment should be combined with a number of psychosocial approaches. The aim is to increase the likelihood of positive outcomes in the domains of both symptom relief and control, as well as functioning. Clozapine is generally recommended as a third-line drug in cases of inadequate response after two adequate trials of other types of antipsychotics.

1.8.1 International guidelines for the treatment of schizophrenia

Numerous guidelines exist for both the prevention and management of psychosis and schizophrenia, with their recommendations applicable to both first-episode cases and subsequent acute episodes of psychosis. Regarding early intervention in psychosis, these guidelines typically recommend a comprehensive array of pharmacological, psychological, social, occupational, and educational interventions. For example, the National Institute of Clinical Excellence (NICE) in the UK advises the use of oral antipsychotic medication in conjunction with psychological interventions (family intervention and CBT)[76]. The choice of antipsychotic medication should be a collaborative decision between the patient and the healthcare professional, involving discussion about the probable benefits and potential side effects of each drug. The same treatment options recommended for the first episode are also suggested for subsequent acute episodes of psychosis or schizophrenia, i.e. oral antipsychotic medication along with psychological interventions, with an assessment of the patient's clinical response and side effects to current and previous medication.

For individuals who have not responded adequately to treatment (treatment-resistant schizophrenia-TRS), the NICE guidelines propose the use of clozapine after sequential use of adequate doses of at least two different antipsychotic drugs. At least one of these drugs should be a non-clozapine SGA. The guidelines for the pharmacological

treatment of first-episode schizophrenia (FES) were compared in relation to key health questions in a study by Keating et al.[110]. Here, concerns about side effects, rather than comparative efficacy benefits, were a significant consideration in the choice of antipsychotics. Clozapine is recommended as the drug of choice in TRS in all the major treatment guidelines for schizophrenia from North America, Europe, Australia and New Zealand[111-113]. These recommendations for the pharmacological treatment of schizophrenia are summarised in the algorithm depicted in Figure 5 (made by the author of this PhD thesis).

1.8.2 Norwegian guidelines for the treatment of schizophrenia

In Norway, the guidelines published by the Norwegian Board of Health Supervision (Statens helsetilsyn) in 2000, were applied in the hospital where the first study of this PhD thesis was conducted[114]. According to these guidelines, clinicians could choose between FGAs and SGAs for the treatment of schizophrenia. The guidelines also stated that "if there is an inadequate response to more than one antipsychotic over a reasonable period of time (3-6 months), the patient should have the opportunity to try clozapine" (translation from Norwegian by the author). An update of these guidelines was published in 2013 by the Norwegian Directorate of Health (Helsedirektoratet)[93]. Various psychosocial interventions were recommended alongside pharmacotherapy in schizophrenia: family interventions, CBT, psychodynamic psychotherapy, milieu therapy, art- and music therapy, physical training and physiotherapy, social skills training, and group therapy. For the pharmacological treatment of schizophrenia, the general principles mirror those found in the NICE guidelines, which are described above. The Norwegian guidelines offered no reason to prefer a SGA to a FGA, based on studies that did not prove any superiority among the various antipsychotics at the group level, regarding efficacy or risk for serious side effects. Ideally, an antipsychotic should be used for at least 4-6 weeks in an adequate dose before drawing conclusions about its efficacy. For patients without a sufficient response to two trials of

antipsychotics in adequate doses, the Norwegian guidelines recommended the use of clozapine, unless serious contraindications are present.

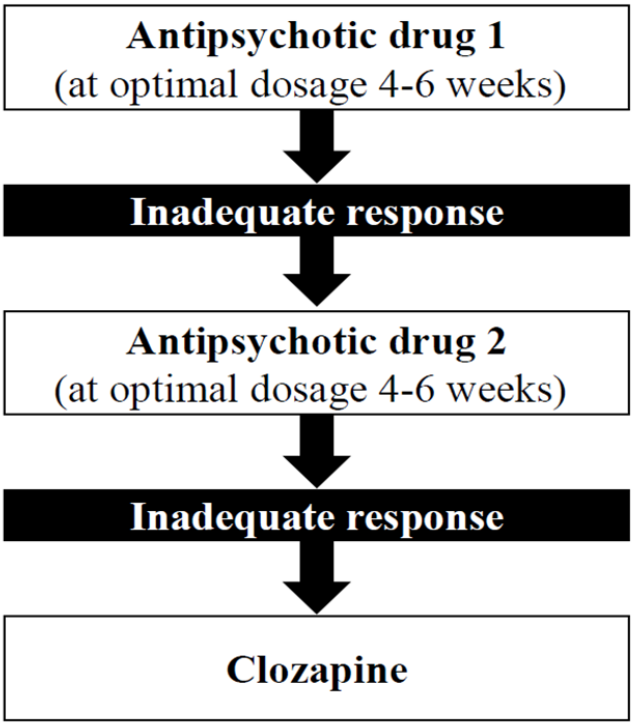

Figure 5. **The algorithm for the pharmacological treatment of schizophrenia. Summary of the recommendations for the pharmacological treatment of schizophrenia, as stated in all major treatment guidelines[76,77,111,113].**

1.9 Response, remission and recovery in schizophrenia

1.9.1 Introduction to the concepts of outcomes in schizophrenia

The estimation of pharmacological treatment efficacy in schizophrenia begins with the assessment of the patients' response, with the further step being the categorisation with respect to remission criteria, and finally, the evaluation if recovery has occured. Response refers to the amelioration of psychotic symptoms, whereas in remission there is a prolonged improvement of core symptoms of schizophrenia (not just the positive ones). Finally, recovery is the most challenging outcome to achieve, as it encompasses functional and social autonomy, in addition to symptomatic remission over an extended period[115]. These critical steps in the course of schizophrenia treatment are outlined in a pyramid-like model, as shown in Figure 6. However, not all of the above-mentioned concepts have been clearly defined. It is important to agree on their definitions and rating methods to enhance the quality of clinical practice and research in schizophrenia.

"Outcome" is defined as "something that follows as a result or consequence"[116]. In the case of schizophrenia, "hard" outcomes like death are not appropriate measures of efficacy. Positive and negative outcomes depend on the course of the symptoms of schizophrenia, and various rating scales have been used to evaluate the treatments[117]. Two of the most frequently used instruments to measure the psychopathology of schizophrenia are the Brief Psychiatric Rating Scale (BPRS)[118] and the PANSS[90]. PANSS is a 30-item, 7-point rating instrument that has adapted 18 items from the BPRS and 12 items from the Psychopathology Rating Schedule (PRS)[119]. These instruments are also used to measure outcomes like response and recovery. Below, I attempt to give a brief definition of the key concepts of response, remission, and recovery in schizophrenia.

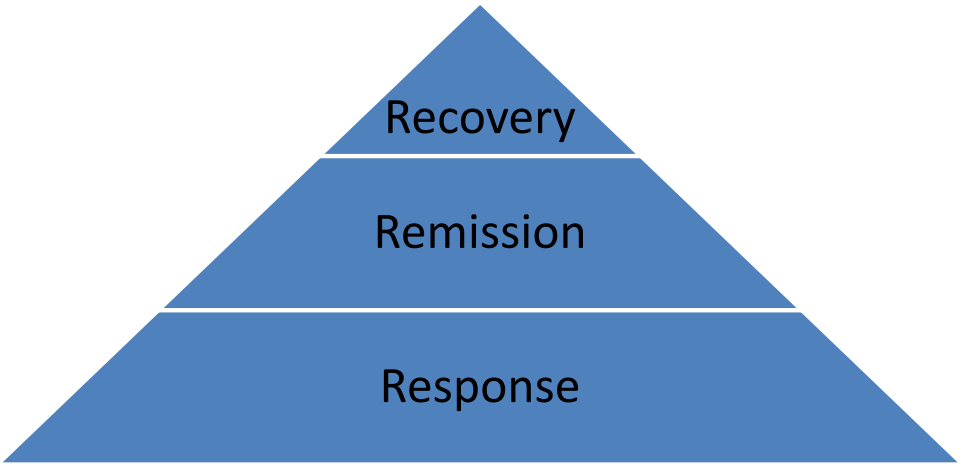

Figure 6. **A pyramid-like model of the steps in the course of schizophrenia treatment**

1.9.2 Response in schizophrenia

For the concept of "response"' there is a lack of consensus on standardised definition criteria. The reduction of the BPRS score or the PANSS total score from baseline has often been used to rate response in schizophrenia, but researchers and clinicians face a challenge in translating the results into clinical practice. It is not always straightforward to assert that a certain change in the BPRS or PANSS score represents a clinically meaningful result. Even if we set a cut-off to define response, the next challenge is that there is not a consensus yet on which cut-off is the most appropriate to use. A number of cut-offs have been used in clinical studies: at least 20%[75], 30%[120], 40%[121], or 50%[122] reduction of the baseline score, but which one is clinically significant? Researchers have proposed to resolve this problem by linking the PANSS and BPRS scores to Clinical Global Impression (CGI) scales[123], which describe the overall clinical state of the patient as an impression made on the rater. The two scales refer to symptom severity (CGI-S) and change/improvement (CGI-I), and feasibility of linking CGI to PANSS values has been demonstrated[124]. For example, a 20% PANSS reduction corresponds

with a CGI-I improvement of 3 ("minimally improved")[125]. The clinical evaluation is very valuable at this point, as the importance of a 20% PANSS reduction, for example, varies when referring to refractory patients versus acutely ill, non-refractory patients. All these challenges make the definition of a "clear-cut" criterion for response in schizophrenia difficult.

1.9.3 Remission in schizophrenia

The concept of "remission" is a general medical term used for both psychiatric and non-psychiatric illnesses. The word "remission" can be traced back to the 13th century AC from Latin and old French and means "relaxation, diminishing" and etymologically "send back, send away"[126]. In cases of illnesses for which treatment is clinically oriented toward "cure", remission may be characterised by the absence of symptoms. For example, remission in rheumatoid arthritis is defined as the absence of fatigue, negligible morning stiffness, and a lack of joint pain, tenderness, and soft tissue swelling, accompanied by a normal erythrocyte sedimentation rate[127]. For non-curable, progressive illnesses, such as multiple sclerosis, remission is not defined as the absence of symptoms but is rather associated with some symptomatic residual dysfunction[128]. To date, remission in psychiatric illnesses like anxiety disorders is not defined by the complete absence of anxious or depressive symptoms, but rather by minimal symptoms with mild disability[129].

Contrary to "response", "remission" in schizophrenia is a well-defined term with widely accepted criteria. These were established in 2005 by the Remission in Schizophrenia Working Group[130], which proposed items for remission criteria both from the BPRS, the PANSS, and the Scale for Assessment of Positive Symptoms (SAPS) and Scale for Assessment of Negative Symptoms (SANS)[131,132]. When using the PANSS to assess remission, the following items are monitored: P1 (delusions), P2 (conceptual disorganisation), P3 (hallucinatory behaviour), N1 (blunted affect), N4

(social withdrawal), N6 (lack of spontaneity), G5 (mannerisms and posturing), and G9 (unusual thought content). For symptomatic remission, maintenance over a 6-month period of simultaneous ratings of mild or less on all items is required, corresponding to a score of three or less in PANSS.

The criteria are often referred to as "consensus remission criteria for schizophrenia". The use of these consensus remission criteria in schizophrenia research makes the various studies on this topic more comparable. On the other hand, the consensus remission criteria refer to a categorical measurement (remission versus non-remission) with a considerable set of requirements to be met. This is, in some cases, disadvantageous when one wants to describe the course of a heterogeneous disorder such as schizophrenia, compared to response, for instance, which measures a percentage of improvement from baseline. It is clear that the terms of response and remission in schizophrenia have their respective benefits and drawbacks.

1.9.4 Recovery in schizophrenia

The concept of recovery is more complex and extends beyond clinical remission, as it also encompasses functional aspects of the patient's life, such as work, social interaction, and academic functioning. Therefore, it is challenging to define recovery and to develop reliable assessment criteria. Most researchers now agree that both clinical outcome and social/functional dimensions should be considered to define recovery. Nevertheless, there are variations regarding the functional outcome domains considered and the duration of time required for the persistence of good outcomes. For example, in the 10-year follow-up study of first-episode psychosis by Hegelstad et al., social functioning embraced work and social interaction, as well as independent living[133]. Both symptom remission and adequate functioning needed to be present for at least one year to define recovery. In a meta-analysis of recovery by Jääskeläinen et al., more stringent criteria were used: positive outcomes related to clinical remission

and broader functioning should be present, and improvement in at least one of these domains should have persisted for at least two years[134]. Although there is still no broad agreement on its definition criteria, recovery should be the ultimate goal for schizophrenia treatment, at least in the first years of the course of illness.

2. STUDY AIMS

The aim of this PhD was to investigate factors in the pharmacological treatment of schizophrenia that could influence and predict both positive and negative outcomes. The objective was to identify areas of improvement in current clinical practice and to propose specific interventions that could enhance these outcomes.

Research questions:

1. To what extent do clinicians adhere to the guidelines for the pharmacological treatment of FES in a cohort of non-remitted patients? (Article 1)
2. What are the response trajectories in an RCT of three atypical antipsychotic drugs, and what factors predict them? (Article 2)
3. What is the remission rate in an RCT of three atypical antipsychotic drugs, and what are the factors that influence and predict remission? (Article 3)

3. METHODS

3.1 Research projects/setting

This PhD was based on data from two research projects: The Early Treatment and Intervention in Psychosis (TIPS) II project and the Bergen-Stavanger-Innsbruck-Trondheim (BeSt InTRo) study.

3.1.1 Article 1- TIPS II substudy

Study design

The first article of this thesis is a TIPS II substudy. TIPS II is a naturalistic, longitudinal cohort of the First Episode Psychosis (FEP) study[135]. It followed the TIPS I study of 1997-2000 wherein patients with FEP were compared between four geographically separate health care sectors in Norway and Denmark[135]. TIPS I early detection program in Rogaland County, Norway, consisted of two major elements: intensive information campaigns and low-threshold detection teams. On 1 January 2002, a year after the information campaigns in TIPS I project had concluded, the recruitment of a new sample of FEP patients commenced. The inclusion criteria, assessment methods, standard treatment protocol, detection teams and follow-up protocol were identical with those of TIPS I, and there was an overlap of the research and clinical personnel. This study, called TIPS II study, took place only in Stavanger area. Our substudy employs an observational cohort design with a one-year follow-up.

A low-threshold early detection team recruited participants by contacting them by telephone both within and outside health care, no referral needed, aided by intensive awareness and information campaigns. All patients were assessed within a week of contact with the psychiatric services and assigned to a two-year standard treatment protocol that included antipsychotic medication, supportive psychotherapy (weekly

sessions with a trained psychiatric case worker), and psychoeducational family work (multifamily groups)[136]. Concerning adverse events (AEs), these were monitored throughout the study period using the St. Hans rating scale[137]. Participants were treated in teams including medical specialists that would swiftly intervene in case of any AEs. These events were, however, not part of our study aims. Participants were treated by clinicians at the local mental health system, and the TIPS personell did not directly administer antipsychotics. TIPS suggested treatment with low dose SGAs, according to the national guidelines for the treatment of schizophrenia[138]. The defined daily doses (DDD) for the antipsychotics administered and the doses for the most used antipsychotics can be found in previous TIPS articles[139,140].

Recruiting centre

The TIPS II study was conducted within the publicly funded specialist psychiatric catchment area services in Rogaland County, Norway, with a total of 370,000 inhabitants[135,141-143]. All patients entering the study provided written informed consent. This substudy comprised data from the time of inclusion until the one-year follow-up and included all eligible participants with FES recruited to the TIPS cohort from January 2002 to August 2013.

Inclusion and exclusion criteria

Participants were between 15 and 65 years, with a diagnosis of acute psychosis, and had to understand and/or speak a Scandinavian language. For a more detailed description of the inclusion and exclusion criteria of TIPS study see Hegelstad et al.[133] and Joa et al[135]. For this substudy, patients were included if they met the DSM-IV[144] criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.

Diagnostic process and outcome measures

Psychosis was defined by a PANSS score of four or more on at least one of the Positive subscale items: 1 (delusions), 3 (hallucinatory behaviour), 5 (grandiosity), 6

(suspiciousness/persecution), or General subscale item 9 (unusual thought content). Participants were assessed by clinically experienced and trained research personnel. Their training was conducted by rating prepared case notes and audio/videotapes. New inter-rater reliability scores were obtained for the TIPS II study for central measures from 17 randomly selected clinical vignettes from the baseline. The reliability of measurements ranged from poor to very good, and the GAF Scale function score (GAFf) was removed from further analyses because of poor reliability. The Structured Clinical Interview for DSM-IV Axis I disorders (SCID)[145] was used for diagnostic purposes, and PANSS was used to measure symptom levels. For the PANSS, we calculated the total and the positive, negative, excitative, depressive, and cognitive component scores.

3.1.2 Articles 2 and 3- BeSt InTro substudies

Study design

The second and third articles are substudies of the BeSt InTro study, a 12-month prospective, randomised, rater-blind, head-to-head comparison of amisulpride, aripiprazole, and olanzapine[146]. The follow-up period was 12 months, with assessment points at baseline and after one week, three weeks, six weeks, three months, six months, nine months, and 12 months.

The participants were recruited from both inpatient and outpatient units, and they were also offered non-pharmacological, psychosocial interventions from their treating clinicians according to the clinicians' evaluation of each case. This information was not registered in our study.

Adverse events were assessed at all visits by means of the UKU Side Effects Rating Scale, patient administered version[147]; open questions from the assessors about any adverse events since last visit; laboratory assessments including ECG, blood pressure

and weight. Furthermore, the clinical monitor screened the medical records for any serious adverse events.

Recruiting centres

The participating study centres were in Bergen, Trondheim, and Stavanger in Norway, in collaboration with the Schizophrenia Research Group in Innsbruck, Austria. Between 20 October 2011 and 30 December 2016, 359 participants were assessed for eligibility, and 144 were included and randomised to one of the study drugs (102 recruited in Bergen and 13 in Stavanger, five in Trondheim and 24 in Innsbruck).

Inclusion and exclusion criteria

The primary inclusion criteria in BeSt InTro were to be of age of 18 years or more, with a diagnosis within the schizophrenia spectrum according to the ICD-10 diagnoses F20–29. For the third article, there was a difference in the inclusion criteria: we excluded patients having a diagnosis of F23 Brief psychotic disorder (n=18), which is characterised by psychotic symptoms that resolve within a month. This decision was made because this study focuses on remission, and due to the time criterion of minimum six months without key psychotic symptoms, which is part of the consensus remission criteria. Another inclusion criterion applied in both substudies was the presence of ongoing psychotic symptoms, as determined by a score of four or more on at least one of the following PANSS items: P1 (delusions), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution), or G9 (unusual thought content).

Exclusion criteria were an inability to understand the native language, organic psychosis due to limbic encephalitis, pregnancy or breastfeeding, hypersensitivity to the active substance or any of the excipients of the study drugs, prolactin-dependent tumours, pheochromocytoma, combination with medications that could induce torsade de pointes, and patients with known risk of narrow-angle glaucoma.

For detailed information about inclusion and exclusion criteria, randomisation and concomitant medications, see the BeSt InTro primary outcome publication[146].

Diagnostic process and outcome measures

Trained clinicians used the Structured Clinical Interview for the PANSS. Satisfactory inter-rater reliability was achieved by training all the investigators conducting assessments and by calibrating them by the PANSS Institute (https://panss.org/).

Other outcome measures included the Calgary Depression Scale for Schizophrenia (CDSS), the CGI-S, and the GAF scale as the average of GAF function and GAF symptom scale score[91].

3.2 Treatment

3.2.1 TIPS II substudy

Participants were required to have not previously received adequate treatment for psychosis (defined as antipsychotic medication of 3.5 haloperidol equivalents for 12 weeks or until remission of the psychotic symptoms) at baseline. After inclusion, as described above, they were offered both supportive psychotherapy, pharmacological treatment with antipsychotic agents and family psychoeducation.

3.2.2 BeSt InTro substudies

Patients were randomly selected to receive one of the studied oral antipsychotics (1:1:1). The attending physician decided the starting dose and this information was available for the patient and the members of the clinical staff, but not for the research personnel who performed the assessments in the study. Each participant was randomised to a sequence of the examined antipsychotic drugs, for example

amisulpride-olanzapine-aripiprazole or aripiprazole-amisulpride-olanzapine. These sequences were put in sealed envelopes, which were opened by the attending physician every time a new patient was included. The first drug in the randomised sequence was offered to the patient, and this drug was the basis of the intention-to-treat (ITT) analyses. If the first drug of the sequence could not be used due to previous issues of inefficacy or tolerability, the patient was offered the next drug in the randomised sequence. The same principle was followed if the second drug also could not be used. The drug that was actually chosen was the basis of the per protocol (PP) analyses. More details about the randomisation and masking can be found in the overview article[146].

The study medications were administered as oral tablets, and the dosing intervals were 50–1200 mg/day for amisulpride, 5–30 mg/day for aripiprazole, and 2.5–20 mg/day for olanzapine. Doses of the study drugs were generally within Summary of Product Characteristics (SPC)-approved ranges, and the defined daily doses (DDD) were about one. The participants of BeSt InTro were asked in every visit if they had taken the study drug. In addition, various serum measurements of the studied antipsychotics were taken, and the pills taken from the returned pill boxes were counted. The serum levels reflected the doses used in a great extent, which may indicate satisfactory compliance[146], but this information was not analysed further in our studies.

For the study in the second article, we calculated the average DDD for the antipsychotics given in each response group. The numbers are as follows: for the Good response group: 1.01 (SD: 0.495), for the Strong response group: 1.22 (SD: 0.583), and for the Slight response group: 1.09 (SD: 0.487). When we used ANOVA to test the three average DDDs, we found no statistically significant difference ($p=0.25$).

The baseline average doses prescribed to the patients were calculated in the third article for the Remitted and Non-remitted group, for each of the three study antipsychotics and with the PP method used (table 1 in article 3). No statistically significant difference was found between the remitted and non-remitted group for each drug.

3.3 Data and variables

3.3.1 TIPS II substudy

Participants were categorised as remitted or non-remitted based on their remission status at the one-year follow-up, as defined by the Remission in Schizophrenia Working Group criteria[130]. Non-remission was identified if patients reported any relapse, defined as a symptom score of 4 or more on the relevant PANSS items over the preceding six months. Participant characteristics at baseline and one-year follow-up were compared, and the pharmacological treatment was scrutinised in detail. The algorithm used in TIPS was recommended as a standard hospital policy and represents a modification of the Norwegian treatment guidelines[114,148].

For the TIPS cohort, patients were assessed at baseline, after 3 months, and at 12 months. For this substudy, only the baseline and 12-month assessments were utilised. For further details about the other demographical and clinical characteristics assessed, please refer to article 1.

At one-year follow-up, the pharmacological strategies implemented for patients were examined in detail. Patient files were reviewed to assess adherence to the treatment algorithm. As per the algorithm, clozapine was considered as the third drug of choice amongst three drug alternatives. All the patient files and clinical descriptions (SCID and PANSS) were reviewed for the presence of remission or relapse during the first year of follow-up. Indications for a switch to clozapine were also closely examined by scrutinising and assessing clinical descriptions, and the pharmacological treatment offered was assessed in detail by registering the different antipsychotics used as first, second, third, or fourth choice. Patient files were utilised to calculate the total duration of antipsychotic treatment, as well as the number of periods with antipsychotic treatment. Additionally, a digital search in all patients' medical files in the hospital data system was conducted, with index "clozapine," "klozapin" (the Norwegian term for

clozapine), and “Leponex” (the brand name for clozapine in Norway). Whenever possible, we sought to identify the reasons for clozapine not being considered or offered to patients.

3.3.2 BeSt InTro substudies

The primary outcome measure in the second article was the response after one-year follow-up, gauged by the change in the PANSS total score during this period. One year corresponds to the minimum recommended time of maintenance treatment with antipsychotic drugs after an acute psychotic episode in patients with schizophrenia[149,150]. The percentage reduction in the PANSS was computed after subtracting 30 points, as this is the minimum score attainable. To calculate response rates, we used the following formula: [(PANSS baseline - 30)-(PANSS follow-up - 30)] × 100/(PANSS baseline - 30)[117]. The change in the PANSS total was calculated for all assessment points.

For the third article, the primary outcome was the remission rate at one year. The consensus remission criteria were used to categorise patients as either “remitted” or “non-remitted”. The remission status was also assessed at all follow-up points, both with and without the time criterion, where applicable. In addition, we examined the impact of each psychotic symptom included in the consensus remission criteria on the remission status of the included patients.

3.4 Statistical analyses

Statistical methods are described in detail in their respective articles. The author of the thesis collaborated with the statisticians about the choice of the statistical methods that were used in the studies, and performed some statistical analyses himself. A concise summary of the statistical procedures followed in each article is provided here.

3.4.1 TIPS II substudy

Participants were classified according to remission status (yes/no) at the one-year follow-up. For the descriptive analyses of the demographical and clinical variables, the SPSS Statistical Program Package (IBM, Armonk, NY), version 20.0 was used. Categorical variables were presented in cross tables and analysed using either a chi-square or Fisher's exact test, as appropriate. All group comparisons of continuous and ordinal data were analysed using the nonparametric Mann-Whitney U test, due to non-normality, as assessed with visual inspection of histograms.

3.4.2 BeSt InTro substudies

For the second article, we fitted a latent class mixed model (LCMM) to our data with the PANSS total score as the dependent variable, time as the independent fixed variable, and subject as a random intercept. This was conducted in R[151] using the LCMM package. We explored models with a varying number of latent classes and different functional forms for the time variables, with the Bayesian information criterion (BIC) and entropy guiding our selection of the best model. A model with a lower BIC and higher entropy indicated a better fit. Differences between the latent classes obtained by the LCMM model were examined. The model best fitting the data had three latent classes and represented time as visit number. The three different response groups were designated as the "Strong Response group", the "Good Response group", and the "Slight Response group". The analysis of categorical and continuous variables and the following comparisons between response groups were performed by using chi-square tests and one-way analyses of variance (ANOVAs) in IBM SPSS Statistics (version 24). If ANOVA tests were significant, we conducted post hoc pairwise analyses using Tukey's test. In comparing antipsychotic drug use among

response groups, patients were classified according to the ITT method, and post hoc pairwise analyses were conducted using Fisher's test.

The patient group was also bifurcated for data analysis: The Good and Strong Response groups were merged into the "Response group", and the Slight Response group was designated as the "Nonresponse group".

In the third article, patients were categorised as "remitted" and "non-remitted" at one-year follow-up, according to the consensus remission criteria as set by the Remission in Schizophrenia Working Group[130]. The remission status was also assessed at all assessment points, both with and without the time criterion, where applicable.

A logistic regression model was fitted to our data to compare the effect of the three studied antipsychotic drugs on remission. Age, sex and medication were used as explanatory variables, and remission status at one year as the outcome variable. Data were analysed in two ways: by dividing the patients into groups according to the medication they were randomised to − ITT analysis − and by dividing them according to which medication they actually received − PP analysis.

Categorical and continuous variables were analysed to compare the remission groups at baseline using chi-square tests and one-way ANOVAs in the SPSS and R programs.

The impact of each PANSS item on remission status was analysed by counting the number of patients with a score of 4 or higher for each of the eight PANSS items at each follow-up point, and the percentage of patients that obtained a score lower than 4 at one year. The same was done at a group level for the positive, negative and general symptoms.

The portion of participants that had their first score as remitted at each assessment point was calculated using the PP dataset and excluding assessments obtained after the participant had stopped using the study medication.

3.5 Ethical considerations, approvals and funding

Both TIPS II and BeSt InTro were conducted according to the World Medical Association Declaration of Helsinki[152].

TIPS II received ethical approval from the Regional Committee for Medical Research Ethics Health Region West, Norway (015.03), as did BeSt InTro (No. 2010/3387-6). Furthermore, BeSt InTro was approved by the Norwegian Medicines Agency. In Austria, BeSt InTro was approved by the Ethical Committee of the Medical University of Innsbruck and the Austrian Federal Office for Safety in Health Care (BASG). In Norway, the Department of Research and Development in Haukeland University Hospital conducted clinical monitoring according to the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP); in Austria, this was performed by the Clinical Trial Centre at the Medical University of Innsbruck. The BeSt InTro study was conducted in compliance with the Norwegian Health Research Act (Helse- og omsorgsdepartementet, 2008). Finally, BeSt InTro is also registered in the Clinical Trials register (ClinicalTrials.gov Identifier: NCT01446328).

TIPS II was publicly funded by Helse Stavanger-Stavanger University hospital. The BeSt InTro study was publicly funded in its entirety by the Research Council of Norway (#213727), the Western Norway Regional Health Trust (#911679, #911820), and the participating not-for-profit hospitals and universities. The author of the thesis is a research fellow with a grant from the Western Norway Regional Health Trust (#912140). Neither the contributing projects (TIPS II and BeSt InTro), nor the work done for this PhD thesis by Petros Drosos, were financially supported by or affiliated in any way with any pharmaceutical company.

4. RESULTS

4.1 Article 1- One-year outcome and adherence to pharmacological guidelines in first-episode schizophrenia: results from a consecutive cohort study

4.1.1 Clinical and demographical characteristics

In total, this substudy included 78 patients, the majority (68%) of whom were non-remitted at one year follow-up. None of the demographical or clinical variables examined demonstrated significant differences between the remitted and non-remitted group.

4.1.2 Treatment with antipsychotic drugs

Olanzapine was the first-choice antipsychotic drug in both groups (nearly in half the cases). Most of the patients in both groups (over 50%) were administered only one antipsychotic drug during the one-year follow-up. Clozapine was offered to three of the non-remitted patients (6%) and ultimately, two of them (4%) received treatment with this drug. None of the remitted patients was treated with clozapine during the first year. In terms of other aspects of the psychiatric treatment provided (total duration of antipsychotic treatment, number of periods with antipsychotic treatment, number and duration of all admissions at the psychiatric department), no statistically significant differences were found between the two groups.

Adverse events were not systematically evaluated in the TIPS II study. In the TIPS I cohort, akathisia, parkinsonism, dyskinesias, dystonia and dysphoria were more often reported in patients on FGAs, and weight gain and sedation were more often reported in patients on SGAs[139]. However, regarding the occurrence of serious adverse events

no deaths occurred during the one-year follow-up, and admissions to hospital were recorded and can be found in table 3 in article 1.

4.1 Article 2- Trajectories of response in schizophrenia-spectrum disorders: A one-year prospective cohort study of antipsychotic effectiveness

4.2.1 Trajectories of response/reduction in the PANSS total score

The model that best suited our data was a three-trajectory model. The majority of the patients belonged to the Good Response group (n=106, 74%) with 59% reduction in the PANSS total score after one year. For the Strong Response group (n=19, 13%), the total reduction in the PANSS total score after one year was 82%. These two groups exhibited a similar improvement in PANSS total score until the six-week follow-up, but the subsequent improvement until one year for the Strong Response group was almost double that of the Good Response group (34% versus 15%). For the third group of patients, the Slight Response group (n=19, 13%), the reduction in the PANSS total score after one year was approximately 14%, which was lower than the reduction the Strong Response group achieved after just one week of treatment.

4.2.2 Clinical and demographical characteristics as predictors of response

We conducted post hoc pairwise analyses to compare the three response groups. No significant differences were identified in terms of years of education or CDSS scores at baseline. Some differences in other characteristics were noted between the groups after the post hoc pairwise analyses, detailed specifically in the article. The PANSS total, PANSS positive and PANSS general average scores at baseline in the Strong Response group were significantly higher than both the other groups. Regarding the

PANSS negative average score at baseline, patients in the Slight Response group had the highest score, while patients in the Good Response group had the lowest (significant difference between these two groups).

Upon merging the Good and the Strong Response groups into the "Response group" and designating the Slight Response group as the "Nonresponse group", we found a significant difference in employment status at baseline: having a regular job was more common in patients in the Response group. Moreover, the CDSS score at baseline was significantly higher in the Nonresponse group, and this was also the case for the averages scores at baseline for both PANSS total and PANSS negative.

4.2.3 Pharmacological treatment in the three response groups

A significantly larger portion of participants in the Strong Response group used amisulpride compared to the portion using amisulpride in the Slight Response group. When the group of patients who used olanzapine was compared with those who used amisulpride, we found a significantly higher proportion of Slight Response group patients in the olanzapine group than in the amisulpride group. The proportion of Slight Response group patients in each medication group was the following: 1/44 for amisulpride, 7/48 for aripiprazole and 11/52 for olanzapine. The proportion of patients who used amisulpride was significantly higher in the Response group than in the Nonresponse group (43/125 versus 1/18).

4.2.4 Serious adverse events and adverse events

No suspected unexpected serious adverse reactions occurred during the BeSt InTro study (this applies for both article 2 and 3). A total of 26 serious adverse events (SAEs) among 20 patients were registered, with no statistically significant differences between the study drugs. Most of these patients (17/20) had only one SAE. Two deaths were

registered (one death by suicide, one unspecific death), in addition to one life-threatening accident, all during follow-up but after discontinuation of the study drug.

Regarding the adverse events as measured by the UKU SERS-Pat, the were no statistically significant differences between the medication groups at 52 weeks. More specifically, participants treated with olanzapine had significantly lower skin rash compared with amisulpride at 52 weeks in both the ITT and PP analyses, and patients treated with aripiprazole had significantly less pruritus compared with amisulpride in the PP analysis. Use of aripiprazole was associated with statistically significantly less weight loss in the last 4 weeks, and less diminished sexual desire compared with amisulpride in the ITT analysis at 52 weeks. Weight, Body Mass Index (BMI), waist circumference, and hip circumference increased in all groups (6,8 kg overall estimated increase in weight [SD 0,7], 2,2 kg/m² overall estimated increase in BMI [SD 0,2], 6,5 cm estimated increase in waist circumference [SD 0,9], and 5,4 cm increase in estimated hip circumference [SD 1,3]). No significant difference between the amisulpride, aripiprazole, and olanzapine groups were found at 52 weeks. These findings are of clinical concern and somewhat surprising given the more benign metabolic profile of aripiprazole as documented in meta-analyses[153].

Serum glucose and QTc interval showed no change during the study period. Serum total cholesterol, LDL cholesterol, and triglycerides were all increased at 52 weeks without group differences in either ITT or PP analyses, except for statistically smaller estimated total cholesterol increase for olanzapine compared with amisulpride in the PP analysis. Serum prolactin increased in all groups, but there were significantly smaller increases in aripiprazole and olanzapine groups compared with amisulpride in the PP analyses.

More information about the serious adverse events and the adverse events can be found in the appendix of the overview article[146].

4.3 Article 3- Remission in schizophrenia spectrum disorders: A randomised trial of amisulpride, aripiprazole and olanzapine

4.3.1 Remission rates and medication status at various follow-up points

One-year remission rate could be determined for 59 patients using the consensus remission criteria and for 49 patients without the time criterion. When using the consensus criteria, 17 patients (29%) were found to be in remission at one year, and the respective remission rate when not using the time criterion was 55%. Without applying the time criterion, the remission rate increased over time and seemed to stabilise between 26 and 52 weeks. A total of 77 patients (61%) dropped out from the study during the one-year follow-up. Two thirds of them were not in remission at the drop-out point. Of the patients who were not in remission at the last observation before the drop-out point, 27% were non-medicated, while the respective number for those who were in remission at the last observation before the drop-out point was 23%.

4.3.2 Predictors of remission

The three antipsychotic drugs were compared to each other with amisulpride as the reference drug. When the ITT model was used, the probability of reaching remission when using aripiprazole or olanzapine was smaller than that for amisulpride (p=0.070 and 0.186 respectively), but not statistically significant. When the PP model was used, the probability of reaching remission for those using aripiprazole was significantly smaller than that for amisulpride (p=0.038). The remission probability for patients using olanzapine was smaller than that for amisulpride, but not significant (p=0.339).

Furthermore, the following two variables showed a statistically significant difference between the two remission groups: patients who had not tried any antipsychotic drug previously (p=0.003) and those with a low negative PANSS subscore at baseline (p=0.025) were more likely to belong to the remission group.

4.3.3 The impact of PANSS items in the remission status

The three positive symptoms included in the consensus remission criteria (P1 delusions, P2 conceptual disorganisation and P3 hallucinatory behaviour), were the most frequent ones with a score of 4 or above at baseline and showed most improvement after one year. The negative psychotic symptom N4 passive/apathetic social withdrawal was the PANSS item with the least improvement when a score of 4 or above was used as cut-off, and this was also the case for the three negative symptoms as a group compared to both positive and general symptoms.

4.3.4 Doses of the studied antipsychotics

We calculated the mean prescribed dose for each antipsychotic drug, both for the remitted and non-remitted group, and for the whole year of follow-up (table 4 in article 3). In the aripiprazole group, the remitted patients used an average dose of aripiprazole, which was almost half of that used by the non-remitted patients, and this constitutes a statistically significant difference ($p=0.0027$).

5. DISCUSSION

5.1 Short summary of main findings

5.1.1 Article 1: The pharmacological treatment offered to the participants of our study was not in complete adherence with treatment guidelines.

In this cohort of 78 patients with FES who completed the one-year follow-up, 32% reached remission according to the consensus remission criteria. For the non-remitted patients, 64% used either none or one antipsychotic drug during the first year and therefore did not commence the second step of the treatment algorithm. Further, only two of the 53 non-remitted patients (4%) were offered clozapine, one as the second antipsychotic drug and the other as the fourth drug in line. These findings suggest a non-adherence to well-known national and international treatment guidelines for schizophrenia.

We have not explored other reasons for not offering more than one antipsychotic or for not considering clozapine in this patient sample, for example if certain medical contraindications were present, therefore we cannot conclude that the clinicians did not follow the guidelines in all cases. On the other hand, we found no written evaluation regarding the use of clozapine in the vast majority of patients.

5.1.2 Article 2: The majority of patients treated with atypical antipsychotic drugs follow a trajectory of good or strong response and the results are more favourable for amisulpride than for aripiprazole and olanzapine.

In our three-trajectory model, 74% of the participants showed good response after one year (59% PANSS total score improvement from baseline), and 13% had a strong

response with a PANSS reduction of 82%. That means that the vast majority of patients in this RCT of three atypical antipsychotic drugs, improved substantially after one year of treatment, confirming the efficacy of antipsychotic drugs.

There were significantly more patients who used amisulpride among those with a good or strong response than those with a slight response. This indicates a favourable result for amisulpride compared to aripiprazole and olanzapine, and that a more frequent use of amisulpride could be beneficial for patients with schizophrenia in need of antipsychotic treatment.

Another finding is the importance of response in the first six weeks of treatment, as patients from the Slight Response group showed no further improvement beyond this point. This result indicates that a switch to another antipsychotic should be considered for patients who do not reach a reduction of approximately 30% in PANSS total score from baseline to six weeks.

Lastly, non-response could be predicted in our study by three variables at baseline: unemployment, depression, and negative psychotic symptoms. This provides clinicians with evidence for areas of intervention with psychosocial and pharmacological tools, both those already established and those which are under research and development, such as newer antipsychotic agents.

5.1.3 Article 3: 29% of the participants reached remission according to the consensus remission criteria at one-year follow-up, and one-year remission was highly correlated with antipsychotic drug naïvety and low negative symptom load at baseline.

The pooled results from the RCT (BeSt InTro) of the three atypical antipsychotic drugs amisulpride, aripiprazole and olanzapine, showed a one-year remission rate of 29%

according to the consensus remission criteria, and 55% when the time criterion of six months was omitted.

While none of the demographic parameters predicted the one-year remission status, antipsychotic drug naïvety and low negative symptoms load at baseline predicted a higher likelihood of belonging to the remission group. Negative symptoms proved the most resistant to treatment when a score of 4 or above was used as a cut-off, with only a 38% change from baseline to one-year observed, compared to 71% for the positive symptoms.

Finally, the use of amisulpride was significantly more likely to lead to remission than that of aripiprazole (in PP analyses). However, this was not the case when comparing amisulpride to olanzapine.

5.2 Discussion of main finding in the thesis

5.2.1 Non-adherence to treatment guidelines for schizophrenia

5.2.1.1 Do the clinicians follow established guidelines in treatment of schizophrenia when prescribing mainly SGAs?

The guidelines for the treatment of schizophrenia offer clinicians knowledge-based information to help them make informed decisions likely to yield positive outcomes. These recommendations represent the views of the institution developing the guidelines and are a result of a careful evaluation of the evidence and knowledge available[76]. Clinicians are strongly encouraged to integrate these recommendations into their treatment approach, taking into account each patient's needs, preferences and values. However, these recommendations are not mandatory, and ultimately the clinician bears the responsibility for providing appropriate, patient-centred care[76].

In our initial study, clinicians predominantly prescribed SGAs, aligning with contemporary national and international guidelines for the treatment of schizophrenia. The NICE guidelines do not differentiate between FGAs and SGAs in the early intervention in schizophrenia, but recommend trying at least one SGA before clozapine is considered for non-responsive cases after two adequate trials[76]. This mirrors the Norwegian guidelines for the treatment of schizophrenia[93,154].

The most recent guidelines from the American Psychiatric Association (APA) state that it is not possible to rank FGAs and SGAs or suggest an algorithmic approach to antipsychotic selection[155]. The reasons include the heterogeneity in clinical trial designs, the limited numbers of head-to-head comparisons of antipsychotic drugs, and the limited clinical data for a number of the antipsychotic drugs. It is not possible, therefore, to note a preference for either FGAs or SGAs, as there is no definitive evidence of the superior efficacy of one antipsychotic compared with another, with the possible exception of clozapine. In addition, there is no reliable way to predict response or risk of side effects with one agent compared with another. Therefore, the choice of antipsychotic should be a result of discussion with the patient about the potential benefits and side effects of the medication options, incorporating patient preferences, past responses to treatment and history of side effects of antipsychotics.

In summary, prescribing mainly SGAs for the treatment of FES complies with national and international treatment guidelines for schizophrenia.

5.2.1.2 Do clinicians commence the first and second step of the treatment algorithm?

Primarily, for patients diagnosed with schizophrenia (paranoid schizophrenia, schizophreniform disorder, or schizoaffective disorder) and not reaching remission at one-year follow-up, it is hypothesised that all should be considered for treatment with antipsychotic drugs. This is the recommended type of treatment, typically in

conjunction with other types of treatment[40]. In our study (article 1), 7.5% of non-remitted patients did not use any antipsychotic agent during the first year and hence did not commence the first step of the treatment algorithm. The reasons for this are unclear; possibilities could include patient unwillingness to be medicated or clinician attitudes towards antipsychotics. Interestingly, a similar rate of 8% of the remitted patients also did not use any antipsychotics during the first year. This finding, albeit based on a very small number of the patients (two), could potentially challenge the general recommendation for using antipsychotics in schizophrenia. Possible explanations could include misdiagnosis of schizophrenia or rare occurrence of psychosis resolution without antipsychotic treatment. Long-term follow-up of these patients could provide further insights into diagnosis stability and remission status.

In terms of the treatment algorithm's first step, 57% of non-remitted patients in our study used only one antipsychotic during the first year and did not switch to a second one despite not reaching symptomatic remission. An additional 15% commenced the second step of the algorithm and used two antipsychotics consecutively during the first year, but did not advance beyond this stage despite non-remission. Only 17% used three antipsychotics consecutively during the first year and hence received treatment compliant with guidelines regarding the switch of antipsychotics in cases of inadequate response.

In summary, the majority of non-remitted patients in this study did not receive treatment beyond the second step of the treatment algorithm. Besides the 7.5% that never tried any antipsychotics, 72% of the patients did not try more than two antipsychotics during the first year. This indicates non-adherence to the treatment guidelines.

5.2.1.3 Do clinicians follow the treatment guidelines when it comes to use of clozapine?

Clozapine was rarely considered and utilised in our initial study. It is hypothesised that all patients failing to attain remission after a one-year follow-up, should proceed to the third step of the algorithm, and therefore clozapine should be considered. These patients are regarded as treatment-resistant, but the definition of treatment resistance is not consistent. The Treatment Response and Resistance in Psychosis (TRRIP) Working Group proposed a consensus-based definition of TRS[156]. They identified TRS as the persistence of significant symptoms for at least 12 weeks, a severity level of at least moderate grade and an impairment of function of at least moderate level. Further evidence of treatment resistance is demonstrated by a prospective antipsychotic trial of at least six weeks at adequate dose, which has not led to symptom reduction exceeding 20%.

Given the total time needed to initiate the first antipsychotic medication, increase the dose to an adequate level, remain at that dose for at least six weeks, evaluate the second antipsychotic option, transition from the first to the second drug, increase its dose to an adequate level and try this medication for at least six weeks (as stated in the major treatment guidelines for schizophrenia[76,77]), it should take no more than six months to complete two adequate antipsychotic trials. The Norwegian treatment guidelines for schizophrenia describe the period of 3-6 months for the trial of more than one antipsychotic, as *reasonable*[93,154]. Beyond that period, the guidelines advocate for the use of clozapine. Despite potential practical challenges and delays in a real-world setting, the patient cohort in our initial study was followed-up by a research team focusing on early intervention in psychosis, and they were treated within a health system in an affluent, developed country where psychiatry is well funded. Therefore, even in the case of FES, endeavouring to reach remission by the use of clozapine should be attainable within the first year of treatment.

In our study, the two patients who were prescribed clozapine, received it as a second and as a fourth choice. This contradicts the treatment guidelines. Nevertheless, some researchers suggest an earlier use of clozapine in the course of schizophrenia.

Clozapine is widely used in China for a variety of psychiatric disorders, and in schizophrenia it is used by some as a first-line treatment[157]. The use of clozapine as a second-line treatment was proposed by the authors of the OPTiMiSE study, a multicentre three-phase switching study in FES. They observed no significant improvements in clinical outcomes when switching antipsychotics and they suggested a single antipsychotic trial for up to 10 weeks followed by the use of clozapine in non-remitted participants[158].

It is unlikely that the use of clozapine was indicated for all of the 53 non-remitted patients in our study, as we did not explore the data regarding adequate dose and duration of use during the previous trials of antipsychotics. These are key elements in the definition of treatment resistance and, therefore, the indication for clozapine use. Moreover, other reasons for the non-use of clozapine may have existed, such as medical contra-indications, refusal from the patients because of the regular blood-monitoring associated with the use of clozapine, or other reasons. However, we found no documented evaluation of these aspects in the patients' journals, indicating non-adherence to treatment guidelines that explicitly recommend considering clozapine for non-remitted patients.

While our findings are derived from a study conducted in a single geographical area in Norway through a specific period of time, the issue of the underutilisation of clozapine is prevalent across different time periods and regions of the world. A review of clinical practice guidelines and clozapine prescribing trends, focusing on publications from 2004 to 2014, revealed that clozapine use is lower than recommended in the USA, UK, Canada, New Zealand and Australia[113]. A recent survey of clinicians' attitudes towards clozapine and its prescription for patients with TRS in Singapore and Hong Kong, demonstrated that the underutilisation of clozapine in TRS remains a concern in both regions[159]. Clinicians' most frequent concerns included the requirement for frequent blood monitoring and clozapine's tolerability and medical complications. Recent studies also highlight the underutilisation of clozapine in Qatar (the first study on

clozapine utilisation from the Middle-East and North-Africa region)[160], Brazil[161] and many other countries[162].

Overall, our study provides evidence of non-adherence to the treatment guidelines in schizophrenia concerning the use of clozapine, although there is no absolute certainty about the indication for its use in all cases.

5.2.1.4 Summary of the non-adherence to treatment guidelines

Non-adherence to consensus-based treatment guidelines represents a challenge for medicine in general, and this issue has been studied also in psychiatry[140,163-165]. Some proposed barriers to guideline adherence are related to the attitude, beliefs and knowledge of the treating physicians. These include lack of awareness or familiarity with the guidelines, disagreement with them, and concerns over control of their professional practice. Other barriers are related to the patients, such as reluctance, insufficient cognitive ability to adhere to the treatment recommended by guidelines, and complexity or lack of clarity within the guidelines. Finally, environmental barriers such as resource availability and facilities have also been proposed[163,166].

Regarding the limited use of clozapine, some specific barriers have been identified[113,167-169]. The use of clozapine carries the risk of potentially fatal adverse effects, such as agranulocytosis[170]. Fear of inducing agranulocytosis may contribute to the reluctance by some clinicians to prescribe clozapine[169], even though studies show that most practitioners are familiar with the guidelines and the effectiveness of clozapine[167]. Current evidence for clozapine suggests that very few patients on clozapine progress from neutropenia to agranulocytosis[171], and that other antipsychotics also pose a risk of agranulocytocis[170]. The mandatory routine haematological control when prescribing clozapine provides an additional safety net, assisting clinicians to identify and manage any side effects that might occur. Moreover, there is robust evidence for both the superior effectiveness of clozapine compared to

other antipsychotics[78,172,173], and the reduced mortality associated with clozapine treatment[79].

In summary, our findings of non-adherence to the treatment guidelines for schizophrenia, and the limited use of clozapine, align with those previously described by other researchers, but remain highly important and clinically relevant.

5.2.2 The majority of patients showed good or strong response to antipsychotic drugs

Antipsychotic drugs therapy is a principal recommendation in Norwegian and international guidelines for schizophrenia treatment[76,77,93,155]. This recommendation is grounded in an extensive body of research conducted over the last few decades on the effectiveness of antipsychotic drugs. Numerous large multi-centre pragmatic RCTs, as well as meta-analyses of RCTs, demonstrate the superior effects of antipsychotics compared to placebo, with some efficacy differences existing between different antipsychotics.

The European First Episode Schizophrenia Trial (EUFEST)[174], an open RCT in patients with first-episode schizophrenia, schizophreniform, or schizoaffective disorder, showed a ≥50% response at one year for patients randomised to amisulpride (67%), olanzapine (67%), ziprasidone (56%), quetiapine (46%) and haloperidol (37%). The proportions for patients in remission at one year, were 40% for amisulpride, 41% for olanzapine, 28% for ziprasidone, 24% for quetiapine, and 17% for haloperidol. The authors concluded that a "substantial proportion" of patients displayed clinically significant response and remission rates after one year of treatment.

In a meta-analysis of 212 RCTs examining acute (6-weeks duration) treatment of schizophrenia or related disorders (including schizophreniform, schizoaffective and

delusional disorder) with data for approximately 43,000 participants, all 15 antipsychotic drugs studied were found more effective than placebo[172]. Another systematic review and network meta-analysis of placebo-controlled and head-to-head RCTs, compared 32 antipsychotics and included 402 studies with data for around 53,000 participants with acute symptoms of schizophrenia or related disorders[78]. All antipsychotics reduced overall symptoms more than placebo, although this was not statistically significant for six drugs. Lastly, a systematic review with pairwise and network meta-analyses of the efficacy of antipsychotics in FES concluded that SGAs were superior to haloperidol for overall reduction of symptoms in the acute treatment of FES, with little difference found among SGAs[175].

In the second study of this thesis, the majority of the participants showed good (59% reduction in PANSS total score) or strong (82% reduction) response after one year. These two groups of participants represent 87% of the total sample, leaving only 13% with a poor response (14% reduction in PANSS total score). This finding corroborates the efficacy of antipsychotic drugs in treating schizophrenia and related disorders, and in our study this applied to both antipsychotic-naïve patients and patients with previous exposure to antipsychotic drugs. It also aligns with the findings from a recent meta-analysis, which examined the variability grade in treatment response in patients treated with antipsychotics compared to those receiving placebo in all suitable RCTs in schizophrenia[176]. The findings from this study point towards an overall greater and more homogeneous response to antipsychotics than that seen with placebo.

Lastly, we can compare the results from the first and the second article. These two articles had different outcomes, as the first one had remission as main outcome, and the second studied response. However, it can be noted that a research project with therapeutic interventions focused on antipsychotics, produces better results than a project with an observational cohort design. It is also obvious that we get a different result when we measure a graded response by PANSS than with a categorical outcome as remission. However, the one-year remission rate was comparable in the first and the third study, although these studies had completely different design. Another difference between the

first and the second study is the much lower drop-out rate in the first study compared to the second one (36% vs 61%). The main conclusion based on the above-mentioned findings is that the design strongly influences the results produced. This includes factors like the observational or the interventional design, the main outcome studied and the duration of follow-up. Also, the results from both studies underline the fact that a large portion of patients with schizophrenia and related psychotic disorders do not achieve remission with non-clozapine antipsychotics. Thus, both increasing the use of the most efficacious antipsychotics through increased treatment guideline adherence, and the development of novel drugs with stronger effect, are needed.

5.2.3 Amisulpride: an efficacious antipsychotic medication, which may be underutilised

In the second study of the thesis, a more favourable overall PANSS response was observed for treatment with amisulpride compared to both aripiprazole and olanzapine. Our third study had remission as the main outcome, and participants treated with amisulpride were more likely to achieve remission than participants treated with aripiprazole, though not when compared to participants treated with olanzapine.

Aripiprazole and olanzapine are among the most used antipsychotics in Norway. According to the most recent report of the Norwegian Institute of Public Health[177], quetiapine is the most frequently prescribed antipsychotic. In 2021, 58% of the persons prescribed antipsychotics received at least one prescription for quetiapine. The use of antipsychotics in general increased from 2017 to 2021 in Norway (1.8% increase in defined daily dose/1000 inhabitants/day and 11.6% increase in the number of individuals prescribed). This was also the case for both amisulpride, aripiprazole and olanzapine, although the disparity between amisulpride and the other two antipsychotics remained significant. Measured in defined daily dose (DDD)/1000

inhabitants/day in 2021, olanzapine was used 24 times more frequently than amisulpride, and aripiprazole was used 7 times more frequently than amisulpride.

DDD is defined by the World Health Oranization as the assumed average maintenance dose per day for a drug used for its main indication in adults, and is utilised for comparisons of drug consumption at an international level[178]. The numbers of patients prescribed olanzapine, aripiprazole and amisulpride in 2021 in Norway, were 19,196, 7,550 and 871, respectively.

The prescription levels for these three drugs stand out in contrast with recent studies demonstrating the potential benefits of amisulpride due to its potent effect. The large-scale clinical study EUFEST[174], conducted across 13 countries, indicated that amisulpride, alongside olanzapine, demonstrated the best outcomes in terms of response, remission and discontinuation for any reason over a year of follow-up. This study compared five antipsychotic medications (amisulpride, olanzapine, ziprasidone, quetiapine and haloperidol) for FES and related disorders. In OPTiMiSE[158], a three-phase switching study undertaken in 14 countries, patients were initially treated with amisulpride for four weeks (phase 1). Those who did not reach remission at four weeks were randomly assigned to continue with amisulpride or switch to olanzapine for six weeks (phase 2). Those patients who still did not achieve remission after phase 2 were given clozapine. After phase one, 56% of patients achieved remission after just four weeks of treatment with amisulpride, indicating a notably favourable outcome for this drug.

In the extensive meta-analysis of trials with 15 antipsychotics conducted by Leucht et al.[172], amisulpride was determined to be the best drug for all-cause discontinuation and the second most effective regarding overall change in symptoms (behind clozapine). Furthermore, amisulpride was ranked as the best drug in terms of sedation and the fifth regarding weight gain. Adversely, amisulpride was among the less desirable antipsychotics in terms of prolactin increase, which is a common side effect. A more recent meta-analysis from the same research group[78], which compared 32 oral

antipsychotics, identified amisulpride as the second most effective medication at reducing overall symptoms in patients with schizophrenia (again behind clozapine), and the most effective for positive symptoms. Amisulpride was also deemed as the third most effective medication at reducing negative and depressive symptoms.

Conversely, another substudy of BeSt InTro examined the sex differences among the three studied antipscychotics[179]. The conclusion was that amisulpride was more effective than the other two antipsychotics for men, but not for women. Furthermore, amisulpride showed more severe side effects for women, indicating that it may not be the first-choice drug for female patients. Nevertheless, this study underscores the necessity of considering the sex differences in larger extent in future medication studies.

The reasons for the underutilisation of an effective antipsychotic drug such as amisulpride remain unclear. The paradox was recently discussed in an article on the website of the American Psychiatric Association[180], where patent and economic issues were proposed as potential reasons for the Food and Drug Administration (FDA) not approving amisulpride for the treatment of schizophrenia. In the United States of America, amisulpride is not registered as an antipsychotic drug, but is used for the treatment and prevention of postoperative nausea and vomiting (in its injectable form)[181]. The article also suggested that "the psychiatric community wants this drug in the United States". As for Norway, although an increase in the prescription of amisulpride as an antipsychotic has been observed in recent years, it seems fair to conclude that the potent treatment effects of amisulpride could be offered to a larger portion of patients with schizophrenia who are in need of antipsychotic treatment.

Our findings indicate that the use of amisulpride is one of the key reasons for the difference in response rates. This could inform potential treatment guidelines with the introduction of amisulpride as a specific recommendation in the first or the second step of the treatment algorithms, except for female patients, as described above. The

development of more personalised treatment guidelines, which take into consideration factors like sex and race, may enhance the outcomes in the treatment of schizophrenia.

5.2.4 The rate of response in the first six weeks of treatment predicts further response to antipsychotics

Determining when to switch an antipsychotic drug in cases of unsatisfactory response is an important clinical question that remains unanswered[182]. In the second article of this thesis, patients in the Slight Response group showed a PANSS total improvement of 16% at week 3, which then dropped to 3% at week 6. From that point to the one-year follow-up, they gained only 11% more improvement from the baseline (totally 14%). This group of patients actually stands out as early as one week into treatment, with a response of 6% contrasting the Strong Response group (17%) and the Good Response group (23%). This disparity becomes even more apparent at week 6: 3% versus 48% versus 45%, respectively.

Both the Norwegian and NICE guidelines for the treatment of schizophrenia recommend a duration of an antipsychotic trial of four to six weeks at an adequate dose[76,93]. The guidelines from the Schizophrenia Patient Outcomes Research Team (PORT)[183,184] and the World Federation of Societies of Biological Psychiatry[150,185] recommend a trial of at least two weeks before switching antipsychotic. However, the body of research underlying these recommendations lack firm conclusions[182]. A large meta-analysis used individual patient data for almost all of the 34 studies examined[182]. The analysis concluded that 90% of patients showing non-response (<20% PANSS or BPRS score reduction) at week 2 will not show much improvement (<50% reduction in PANSS or BPRS score) at endpoint (4-12 weeks), 88% will not achieve symptomatic remission at endpoint, and 55% will not even minimally improve (<20% reduction in PANSS or BPRS score). The patients in these studies should have received target doses of antipsychotics for at least two weeks. The authors suggest that patients not

improving after two weeks on an adequate dose of antipsychotic should be switched to another antipsychotic, saving them from unnecessary long-term exposure to an antipsychotic unlikely to help them. These suggestions are incorporated in the guidelines of the APA[155], which further recommend monitoring the patient's clinical status for 2-4 weeks on a therapeutic dose unless uncomfortable side effects are present. However, a large switching study, OPTiMiSE[158], concluded that switching antipsychotics did not improve clinical outcomes in non-remitted patients after their first antipsychotic drug trial, and proposed a single antipsychotic trial for up to 10 weeks, followed by clozapine use in non-remitted patients.

A clear recommendation about the timing of switching antipsychotics in cases of non-response cannot yet be given based on solid evidence. Parameters that need to be clarified include the definition of non-response that qualifies for an antipsychotic switch and the time required to titrate an antipsychotic drug to a therapeutic dose. The rate at which clinicians titrate antipsychotics varies, and in the above-mentioned meta-analysis, most studies followed a quick titration schedule, with target doses reached within three days. Taken these parameters into account, our findings indicate that non-response (<20-30% reduction in PANSS total score) after six weeks of an antipsychotic trial predicts further non-response, and clinicians should consider switching antipsychotics at that point. An antipsychotic trial on an adequate dose for at least two weeks should be warranted. However, our finding from the third study, that a substantial proportion (18/60) of remitted patients achieved their score of remission after week 6, indicates that in some cases the antipsychotic effect of the drugs emerges at a later point. Clearly, predictors of late response versus non-response would also be very valuable in the treatment of patients with schizophrenia-spectrum disorders.

5.2.5 Unemployment, depression and negative psychotic symptoms predict poor response

Longitudinal studies performed over several decades have attempted to identify clinical predictors of outcomes in schizophrenia[186]. However, the heterogeneity of schizophrenia and the high frequency of unfavourable outcomes mean that a specific pattern of disease progression remains elusive[187,188]. Understanding prognostic factors may facilitate the identification of treatment and patient factors more likely to result in improved outcomes, thereby avoiding multiple, unnecessary treatment trials.

Most predictors of poor outcomes are non-modifiable, such as male sex, younger age at disease onset, poor premorbid adjustment, and severe psychopathology. Modifiable predictors of negative outcomes include longer duration of untreated illness, non-adherence to antipsychotics, comorbidities (particularly substance use disorders), lack of early antipsychotic response, and a lack of improvement with non-clozapine antipsychotics, predicting a response to clozapine.

A review of clinical predictors of therapeutic response to antipsychotics in schizophrenia categorised them into patient, illness, treatment and environmental variables[186]. Another review examining treatment response in FES, reported favourable response rates ranging up to 80%, with varying response time[188]. Short duration of untreated psychosis and good premorbid adjustment were two of the most reliable clinical predictors of response to treatment. In a review of the long-term outcomes in schizophrenia, several predictors of poor outcome were identified, with the most frequently reported being the male sex and pronounced negative symptoms[187].

In the second article of this thesis, we identified three predictors of non-response to the three studied antipsychotics: unemployment, depression, and high burden of negative symptoms at baseline. Unemployment is a modifiable predictor, but studies have not yet demonstrated a causal relationship with outcomes in schizophrenia[189,190]. Employment status is seldom mentioned as a predictor of response in studies and reviews on this topic, for both short-term and long-term outcomes in schizophrenia[186-188]. However, employment status is also an important functional outcome in schizophrenia. Although there are different ways to define recovery in schizophrenia,

the patient's employment status is included in almost every definition of recovery. Follow-up studies have shown that having a job predicts recovery[191,192]. The results from our study indicate the positive effect supported employment may have on the course and outcome in schizophrenia, both short- and long-term.

Depression is common in schizophrenia and associated with negative outcomes[193,194]. It can occur in the prodrome[195], acute[196] and postpsychotic[197] phase of the illness and is now recognised as a distinct dimension of psychosis, thereby challenging the Kraepelinian dichotomy between schizophrenia and affective psychoses[198]. The findings from our study indicate that severe symptoms of depression at baseline can predict response rates during the one-year follow-up. This underscores the need for a thorough evaluation of depression in the early stages of schizophrenia. Detection and appropriate treatment of depression may improve overall outcomes in schizophrenia.

Negative symptoms have been found to predict poor outcomes in schizophrenia, with special evidence for recovery and long-term functional outcomes, but this has not been demonstrated for the relative treatment response as a short-term marker of efficacy[186]. This may indicate the association between negative symptoms and functioning, reflected in interpersonal behaviour and relationships, social and work skills etc.[199], while score changes in scales like PANSS, BPRS or CGI are more influenced by positive symptoms. Consequently, these score changes fail to reflect the poor response of negative symptoms, which are relatively unresponsive to current treatments. The findings from our study, which suggest a predictive value of baseline negative symptoms for response trajectories through a one-year follow-up, diverge from previous research in terms of also demonstrating negative symptoms as a predictor of short-term outcome. This underlines the significance of negative symptoms in the course of schizophrenia and highlights the need for the development of new therapeutic agents targeting these symptoms.

5.2.6 The one-year remission rate was 29% when using the consensus remission criteria, and 55% when the time criterion was omitted

The one-year remission rate of 29% found in the third article of this thesis is relatively low compared with that found in other remission studies. In a systematic review from 2012, 27 studies in schizophrenia were included, and the one-year remission rate ranged from 17% to 78% using consensus remission criteria[200]. In another review, which included 30 studies published after the introduction of the consensus remission criteria in 2005, the authors calculated a total one-year remission rate of 52% for FES when using the full criteria, and 68% when the time criterion was not used[201]. For patients with multiple episodes, the respective numbers were 38% and 55%. Another review reported remission rates in schizophrenia ranging from 35% to 50%[186]. Individual studies reported one-year remission rates of 19% for FES and 23% for non-FES (without using the time criterion)[202], and 81% for FES (without the time criterion)[203]. A remission study of our group (article 1) found a one-year remission rate of 32% for patients with FES, using the full remission criteria[204].

Comparisons between studies are difficult due to their heterogeneity. A number of factors contribute to this phenomenon: (i) the selection of population samples (acute versus chronic patients, FES versus non-FES, diagnoses other than schizophrenia spectrum, comorbidity with other psychiatric disorders, substance use, etc.), (ii) the duration and frequency of follow-up, (iii) the drop-out rate, and (iv) the use (or non-use) of antipsychotic drugs[200,201].

Another important factor is the remission criteria applied. Despite the wide dissemination and utilisation of the consensus remission criteria, not all remission studies adhere to them, particularly with regards to the six-month time criterion, so that they calculate remission in schizophrenia without a specified period of maintenance[201]. The clinical usefulness of such results is unclear. Unique to the third article of this thesis, the consensus remission criteria were used both with and without the time

criterion, a methodology infrequently employed in other studies. This approach allowed us to observe the significant impact of the time criterion on the one-year remission rate, which notably doubled when the time criterion was omitted. Further, we calculated the remission rate at various follow-up points and observed a substantial range in the time to remission. More studies on remission in schizophrenia should be performed using the full consensus remission criteria, to increase the clinical utility and generalisability of the studies.

The remission rate increased substantially over time when the time criterion was used, but the value of this finding is questionable. It is obvious that very few patients could reach remission during the first six months of the follow-up, since the needed time to sustain symptomatic remission is six months. The fact that most of the patients who dropped out were non-remitted, contributes to the increasing remission rate over time. Another factor is that the period of six months is a sizeable fraction of the follow-up time in this study (50% of the 12-months follow-up), which obviously influences the remission rate in the BeSt InTro study.

Although we used strict consensus remission criteria, it is concerning that only 29% of the participants reached remission after one year, despite participating in a closely monitored antipsychotic trial in a country with substantial funding for psychiatric practice and research. The clinical characteristics of the patients at baseline (for example high burden of negative symptoms) may be among the contributing factors to the relatively low one-year remission rate. However, it must also be concluded that the current treatment options for patients with schizophrenia are far from ideal, underscoring the need for further research to develop novel, more effective treatments.

5.2.7 Antipsychotic drug naïvety and low negative symptoms at baseline predicted remission

In the third article of this thesis, none of the demographic variables were found to predict the one-year remission status. However, two clinical parameters emerged as significant predictors: antipsychotic drug naïvety and low negative symptoms load at baseline.

There are various studies examining predictors of outcome in schizophrenia, including those specifically focused on remission, and there are two reviews summarising the results from those studies[186,201]. Antipsychotic drug naïvety is not cited as a predictor in these reviews, and in one remission study for early psychosis, previous antipsychotic exposure was studied, but it did not prove statistically significant[205]. Hence, our study offers a fresh, interesting finding in this area. The clinical implications could include heightened vigilance when treating new, antipsychotic naïve patients with FES, since they may have higher chances of responding to antipsychotic drugs and achieving remission. Conversely, patients with prior antipsychotic trials warrant a thorough evaluation of subsequent trials, along with a review of previous trials to assess their adherence to the guidelines.

Regarding the predictive value of baseline negative symptoms for remission, existing studies show that negative symptoms predict poor outcomes in schizophrenia[205,206]. Our studies (articles 2 and 3) on the same patient sample, demonstrate that high negative symptoms at baseline predict both poor response and non-remission at one-year follow-up. Negative symptoms were the most resistant to antipsychotic treatment, contributing as much to non-remission as the positive symptoms at one year. At this point, 15 patients (29%) scored four or higher on at least one positive symptom, and 14 patients (27%) scored similarly on at least one negative symptom. At baseline, the number of patients scoring four or more on at least one of the core positive symptoms was more than double than those with similar scores in negative symptoms (124 versus 55). The percentage change of patients with a score of four or higher from baseline to one year was 71% for the positive symptoms and 38% for the negative symptoms. This finding underscores the limited efficacy of the studied antipsychotics, particularly for

the negative symptoms in schizophrenia, but also for the positive ones. Factors that could enhance the effect of the antipsychotic treatment include better use of the established antipsychotics (optimalisation of duration of use and dosage), improved adherence to antipsychotics and the development of new therapeutic agents specifically targeting the negative symptoms.

5.2.8 The unmet need for the development of new pharmacologic agents for the treatment of schizophrenia

Our finding (article 3) of the proportion of 29-55% of participants reaching remission (depending on the inclusion of the time criterion), illustrates the limited efficacy of three representative atypical antipsychotic drugs, specifically in the domain of negative psychotic symptoms, but also that the effect on positive symptoms is less than perfect. Consequently, there is an urgent need to develop new pharmacological strategies for the treatment of schizophrenia, and a few of the more promising novel approaches will be briefly discussed.

Putative effects of proposed novel treatment targets in schizophrenia focus on *regulating dopamine function*, rather than relying solely on *post-synaptic dopamine blockade*[207]. Several new therapeutic agents have been studied in recent years and are currently under development, but their clinical usefulness remains to be determined. Low doses of apomorphine have been used to activate dopamine autoreceptors, which could reduce striatal hyperdopaminergia, whilst boosting dopamine function in cortical regions, and therefore, treat cognitive symptoms[208]. Phosphodiesterase (PDE) inhibitors may boost D1 signalling whilst reducing D2 signalling[209,210].

Another area of interest is the upstream glutamate and GABA systems that regulate dopamine neurons. Co-agonists at the NMDA receptor, such as serine and D-cycloserine, may be effective in schizophrenia, although the results of clinical trials to

date have been inconsistent[211]. GABAergic hypofunction is also thought to play a role in the dopamine dysregulation in schizophrenia, and results from studies in mice suggest that alpha 5 subtype selective GABA agonists might be effective for schizophrenia[212].

Cannabis use has been linked to increased risk of developing psychosis[213], which has led to greater interest in the cannabinoid system. Cannabidiol (CBD), a phyotocannabinoid from the cannabis plant, may inhibit fatty acid amid hydrolase (FAAH), an enzyme that breaks down N-arachidonoylethanolamine (AEA), and therefore enhances the inhibitory action of AEA on dopamine release, with a potential antipsychotic effect[214].

The link between the immune system and schizophrenia has been widely studied in recent years, leading to the proposal of new immune-regulating agents as add-on antipsychotic treatment[56]. These include neurosteroids, statins, N-acetyl cysteine, glitazones and melatonin[68]. Another interesting agent currently under investigation is tocilizumab, a humanised monoclonal antibody targeting the IL-6 receptor. This agent inhibits IL-6 signalling and is licensed for the treatment of rheumatoid arthritis. A targeted, experimental medicine, placebo-controlled study is currently ongoing, where patients are randomised to tocilizumab and placebo[215].

Two of the most promising new pharmacological agents are the trace amine type 1 receptor (TAAR1) agonists and the muscarinic agonists. TAAR1 agonists may be able to target striatal hyperdopaminergia, as these receptors respond to endogenous amines and control dopamine neurons by feedback[216,217]. There are 5 different muscarinic receptor subtypes (M1, M2, M3, M4 and M5) that are expressed in a wide variety of tissues in the brain and periphery[218]. For schizophrenia, the M1 and M4 receptors are of interest. The M4 autoreceptor agonism modulates mesolimbic circuits, inhibits acetylcholine release and indirectly decreases dopamine activity. The M1 agonism modulates mesocorticolimbic circuits and decreases dopamine activity by increasing GABA and decreasing excitatory glutamate. Presently, there are several muscarinic

agonists in development. KarXT (xanomeline-trospium)[219,220] has been investigated in a phase-3 study showing significant reductions in PANSS positive subscale at week 5 compared to placebo, without being associated with side effects like weight gain, Parkinsonism, dystonia, akathisia, or sedation.

Overall, there are several novel therapeutic agents under development for the treatment of schizophrenia. Some of these have mechanisms of action that differ from the available antipsychotics, which primarily act directly on the dopamine receptors. For example, muscarinic agonists do not target the dopamine receptors directly, but rather indirectly regulate the dopamine activity, indicating that dopamine appears to be a central neurotransmitter in the pathophysiology of schizophrenia.

5.3 Strengths and limitations

5.3.1 Article 1

For the first article, the strengths include the robust design of the study with stringent criteria for both inclusion in the study and definition of remission. All the consecutive patients with FEP in the catchment area were followed up for one year. There was also access to all the medical files of the included patients since these were to be found in the electronic journal system of the hospital.

One major limitation of the study is the lack of information about the attitudes of both clinicians and patients regarding the offered medication. This restricts any conclusions about the limited adherence to treatment guidelines, including the underuse of clozapine. Our findings were based on the search of certain indexes in the medical files. In case the clinicians had assessed the use of clozapine and found that its use was not possible for various reasons, but not documented it in the patients' medical files, this information could not be reachable for us.

Another limitation is that the study enrolment period took place several years ago, and the findings about the prescription of antipsychotics may not reflect the current practice

in Norway. The latest official drug consumption report for Norway covers the years 2017-2021 and uses data from the Norwegian Drug Wholesales Statistics and the Norwegian Prescription Database[177]. From the four most frequently used antipsychotics in our study, the use of three of them (olanzapine, quetiapine, aripiprazole) increased from 2017 to 2021 in all parameters (DDD/1000 inhabitants/day, number of individuals, and prevalence per year). The use of quetiapine was increased in a greater extent than the other two antipsychotics. The use of risperidone decreased in terms of DDD/1000 inhabitants/day, but increased regarding the number of individuals prescribed risperidone, while the prevalence remained the same from 2017 to 2021. For clozapine, there was a slight increase of the total individuals prescribed this medicine (from 2.651 in 2017 to 2.771 in 2021), but the DDD/1000 inhabitants/day decreased. The prevalence remained stable (0.5/1000). The statistics of the prescription of medicines in Rogaland County (where our study was conducted) show that the prescription of antipsychotics in general increased from 2013 to 2020, while the prescription of clozapine in the same period declined. These findings point towards a general slight increase of the use of antipsychotics in Norway, with the exception of quetiapine, which is prescribed much more frequently and is by far the most frequently used antipsychotic drug in the country. However, it is a well-known fact that quetiapine is used on additional indications, not just to treat psychoses. The use of clozapine remained stable in national level over the last years, but declined in Rogaland County from 2013 to 2020, which indicates a possible underuse also nowadays in Norway.

Lastly, in this article we analysed our data using standard univariate analysis. As is common practice, univariate analyses were first performed to explore differences on single variables. Since there were no univariate effects, multivariate follow-ups were deemed unnecessary. Further, the low sample size could have led to multivariate overfitted models.

5.3.2 Articles 2 and 3

The general strengths of BeSt InTro include that it is the first head-to-head comparison of amisulpride, aripiprazole and olanzapine in a randomised, pragmatic efficacy trial. This direct comparison of these agents provides some clear advantages compared to network meta-analyses. Moreover, our study was industry-independent and rater-blind. Another strength of the study was the frequent follow-up points, particularly in the first weeks of treatment, which are quite important, as well as the use of well-validated instruments to describe our main parameters, such as PANSS, CGI and CDSS. Lastly, the follow-up of the study was relatively long (12 months), which is longer than other response studies that examined shorter periods with antipsychotic drugs[221]. The design chosen for the BeSt InTro study was a pragmatic one to mimic the everyday clinical practice: broad inclusion criteria, few exclusion criteria, open-label treatment administered by the treating psychiatrist in collaboration with the patient, and long follow-up.

The limitations of our studies include that there was no placebo control; therefore, we must interpret our results with caution. In addition, the design of the BeSt InTro allowing participants to switch antipsychotic drug during the study period poses some challenges. Also, some of our participants entered the study having tried other antipsychotic(s) previously, while the rest were antipsychotic-naive. We also included both first-episode and multiple-episode schizophrenia patients. These parameters may represent a bias into the interpretation of our results, but they add to the pragmatic quality of our study, as it is closer to everyday clinical practice.

Secondly, the drop-out rate in the BeSt InTro studies was high (around 61%) and this represents a major limitation for the interpretation of our results. The fact that around two thirds of the patients who dropped out were not in remission at drop-out point, may contribute to the increasing remission rate over time (when not using the time criterion). Since we chose to present results only for patients for whom we had clinical data at these points (when not using the time criterion), we believe that these findings represent the actual status at certain follow-up points. Moreover, the drop-out rate in our study is comparable to that found in other large randomised antipsychotic drug

trials, such as the CATIE study (74% before 18 months)[222], while the EUFEST study had lower attrition (41.6% before 12 months)[223]. However, analyses of attrition indicated that the sample after 52 weeks was representative of the sample at baseline. The relatively small sample of patients with data on remission at one year is another limitation of our studies, and it can be explained partly by the high drop-out rate. Regarding the third study, the fact that remission is more difficult to achieve than response, as well as the relatively small sample of patients in our study, may contribute to reduce the chances of finding possible differences among the studied drugs. Moreover, results for predicting remission when using amisulpride only reached statistical significance using PP and not ITT analyses. This finding may indicate that PP analyses are more sensitive than ITT analyses in showing differences among medicaments. However, it also weakens the conclusion of a possible superiority of amisulpride in efficacy compared to aripiprazole and olanzapine, because the PP groups are not completely randomised. Larger multicenter studies are needed for the validation of our results. Lastly, most of the included patients were white Europeans (88%) and men (65%). Our results are therefore not generalisable to all human populations, regarding both race and sex.

6. CONCLUSION

The central research questions throughout this thesis revolve around the outcomes of current antipsychotic treatment in patients with schizophrenia spectrum disorders and the reasons for the lack of improvement.

Our first research question examined the guidelines for the pharmacological treatment of schizophrenia, and we found that these were not fully adhered to. Clinicians did not initiate all the steps of the proposed treatment algorithm, as many non-remitted patients had only used one or two antipsychotic drugs during the one-year follow-up. Furthermore, our findings indicated that clozapine was underutilised, since a proportion of the non-remitted patients were likely treatment-resistant, and clinicians should have proceeded to the third step of the treatment algorithm, which recommends the use of clozapine. Ideally, clozapine should have been evaluated for all non-remitted patients in our sample, but according to the hospital's journal system, this was not done, amounting to malpractice.

For the second research question, we identified three response trajectories in an RCT of three atypical antipsychotic drugs. The vast majority of the participants (87%) showed at least a good response to the antipsychotic drugs used in the study, which encourages further prescription of established antipsychotics for the treatment of schizophrenia. Unemployment, depression, and high load of negative psychotic symptoms at baseline predicted poor response, and the response rate in the initial six weeks of treatment predicted further response through the one-year follow-up.

Remission, as studied in the third article, pertained to the third research question. The one-year remission rate in an RCT of three atypical antipsychotic drugs was 29%, closely mirroring the one-year remission rate found in another pasient sample studied in our first article. The one-year remission rate nearly doubled when the time dimension in the consensus remission criteria was omitted, showing the significance of this

criterion. This also emphasises the importance of using consistent consensus criteria in remission studies to ensure comparability. Remission at one year was predicted by antipsychotic drug naïvety and low negative symptoms at baseline. Negative symptoms are challenging to treat with currently available antipsychotic drugs, highlighting the urgent need for the development of new agents specifically targeting this domain of symptoms.

Another important finding from our RCT (articles 2 and 3) was the discrepancy in drug effectiveness and the favourable results for amisulpride compared to aripiprazole and olanzapine. Considering that amisulpride is not commonly used in Norway, these results challenge the current clinical practice and propose a change that could result in improved outcomes in schizophrenia treatment. However, sex differences need to be considered.

7. FUTURE PERSPECTIVES

While working on this thesis, I endeavoured to find answers to certain research questions, as stated above. As a clinician, I also aimed to discern the clinical implications of the study findings. My goal was to identify areas where the current clinical practice could be enhanced and to propose interventions to ameliorate the outcomes in schizophrenia treatment.

In analysing the potential reasons for lack of improvement in schizophrenia treatment, the following questions and answers were generated:

1) Do the clinicians apply evidence-based treatment?

Our findings indicate that there is a substantial scope for improving clinical practice by enhancing adherence to national and international guidelines for schizophrenia treatment. While the efficacy of antipsychotics in certain domains of the psychopathology of schizophrenia is indisputable, it is imperative that their correct use is ensured. Appropriate switch of antipsychotic drugs after inadequate response, and thereby averting unnecessary delays in establishing effective treatment, along with the more frequent use of clozapine when indicated, are critical factors that would enhance treatment outcomes. The guidelines for the treatment in schizophrenia can provide valuable assistance to clinicians. Although studies have shown that the majority of clinicians are cognisant of these guidelines, the findings from our study (in line with other studies) indicate that adherence to the guidelines is not satisfactory (article 1). Clozapine is unequivocally shown as the most effective antipsychotic drug, at least for TRS. Our study indicates that clozapine is underutilised (article 1), which aligns with several previous studies.

For non-clozapine antipsychotics, recent meta-analyses have shown amisulpride to be potentially the most efficacious drug, which is also corroborated in our studies, particularly for men (articles 2 and 3). However, data from the Norwegian authorities show that the number of patients prescribed amisulpride is low compared to many other antipsychotics. The paradox of the underutilisation of the two most effective antipsychotics must be addressed and measures have to be taken in order to refine clinical practice. Better information and education of both health personnel, patients, and their families about these aspects could contribute to increasing the prescription of clozapine and amisulpride.

2) Are there areas in the psychopathology of schizophrenia where we do not have satisfactory treatment as for today?

The answer to this question is affirmative. Our study (article 3) unambiguously demonstrated that negative symptoms were, to some extent, resistant to treatment with the antipsychotics used in this study. Positive symptoms were more prominent at baseline, but significant improvement (albeit not complete) was observed after one year of treatment. Additionally, both studies (articles 2 and 3) identified negative symptoms at baseline as a predictor of both poor response and non-remission. The challenge of treating negative symptoms in schizophrenia highlights the pressing need for new antipsychotic agents that specifically target this symptom domain. Emerging pharmacological agents show promise and are currently under development; it is hoped that some of them will be integrated into the available treatment arsenal for schizophrenia. Possessing a broader range of pharmacological agents that target various aspects of schizophrenia's multifaceted psychopathology could help realise the aspiration for personalised medicine in psychiatry. By mapping the symptom, as well as the physical profile of the individual, future psychiatrists will be better equipped to select the appropriate drugs to assist the patient in achieving symptomatic and functional improvements, and, ideally, recovery from the severe disorder known as

schizophrenia. The development of clinical and biological markers for outcome in schizophrenia will hopefully foster a more personalised approach in the field and enhance the outcomes.

Source of data

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