Depressive symptoms in psychotic disorders:

Trajectories of depression and antidepressive effectiveness of antipsychotic medication

Eirik Kjelby

Thesis for the degree of Philosophiae Doctor (PhD)
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Introduction/preface

Since my first encounter with psychiatry during medical school; meeting and interviewing patients in student teaching groups, I felt curious about the field. During intern practice I felt even stronger that in practicing medicine I wanted to delve deeper into the stories of the persons behind the illnesses, partially distancing myself from the medical school views focusing on particular pathology or diagnostic subgrouping. During jogging sessions in the mountains of Sogn and Fjordane as intern I decided that I would apply for residency within psychiatry. Psychiatry residency fascinated me from the beginning with the complexity of the field, the gloomy but captivating expression of illnesses in patients I met, the rewarding feeling of working in team with motivated and competent colleagues and most importantly, the immense satisfaction in being able to contribute to the vast improvement, sometimes remission, of severe psychiatric states. Thus, I felt useful in the clinical work and had no thoughts or aspirations to enter the research field. Not until my good colleague Rune Kroken started to motivate me to attempt psychiatry research during my residency. The way my emotional apparatus is constructed, I was not immediately motivated, but with skilled continuous refills of motivation from Rune I realized that I could not let go of an opportunity to experience how delving into research could foster improved clinical skills and vice versa and strengthening the competence of the university hospital. Suddenly in the skilled hands of my supervisor Erik Johnsen, research turned out to be just what I hoped and Rune had told me.

Abstract

Background: Depressive symptoms are common in psychotic disorders and contribute to impaired functioning, a poorer quality of life, elevated relapse rate and suicide risk. Depression in schizophrenia may emerge as part of the prodromal phase, preceding and during a psychotic episode and as post-psychotic depression. Early studies indicating dysphoric effects of antipsychotics have been superseded by studies demonstrating antidepressive properties for several atypical antipsychotics. Atypical antipsychotics may exert their antidepressive effects through antagonism at serotonergic $5HT_2$ receptors, agonism at $5HT_1$ receptors, antagonism at adrenergic α_2 receptors and inhibition of trans-membrane monoamine transporters. Guidelines for the treatment of depression in psychotic disorders remain unclear due to unresolved issues related to among others, the heterogeneity of depression in psychosis, thus more studies are needed. To investigate differences in antidepressive effectiveness, we conducted comparative trials of atypical antipsychotics funded independently of the pharmaceutical industry.

Methods: Change in depressive symptom sum score measured by Calgary Depression Scale for Schizophrenia was investigated in two separate randomized clinical trials, analysed by means of Linear Mixed Effects models and Latent Growth Curve modelling. Trajectories of depressive symptom change were identified with Growth Mixture Modelling.

Results: In the first paper we found depressive symptom reduction that was not significantly different between the atypical antipsychotics olanzapine, quetiapine, risperidone and ziprasidone in a 24-month, industry-independent, randomized trial of 226 patients acutely admitted with psychosis, although olanzapine had the smallest reduction and risperidone the greatest. There were no significant effectiveness differences in the patients with most pronounced depression neither. A much larger drop-out than assumed reduced statistical power. Still, effectiveness differences were smaller than considered clinically relevant.

In the second paper from the same trial we investigated heterogeneity in treatment response and found three depression-trajectories: one depressed and treatment refractory group (14.7%), one group with limited depressive symptoms (69.6%) and a third depressed but early responding group (15.7%). A reduction of positive psychotic symptoms predicted depression improvement. Post-psychotic depression did not emerge in patients that were not depressed in the acute phase and we could not identify differentiating characteristics of the depression trajectories.
The third paper investigated the antidepressive effectiveness of the atypical antipsychotics amisulpride, aripiprazole and olanzapine in a second randomized clinical trial. In 144 patients no between-drug differences in depressive symptom reduction were found, although the amisulpride group had the greatest depressive symptom reduction. The majority of depressive symptom reduction occurred within 6 weeks. No antidepressive effectiveness differences between the study drugs were found in the group with most pronounced depression, neither. Statistical power was smaller than power-analyses indicated due to discrepancies between presumed and actual study characteristics.

Conclusion: We conclude that the net effectiveness of atypical antipsychotics during and following psychotic episodes on group-level is antidepressive and not depression-inducing. Since no head-to-head antipsychotic antidepressive differences were found, we can make no recommendations concerning choice of any particular atypical antipsychotic for targeting symptoms of depression in patients acutely admitted with psychosis. The treatment-refractory patients are candidates for enhanced anti-depressive treatment, for which current evidence is limited. For a substantial portion of patients treatment as usual of the psychotic episode was sufficient to reduce acute-phase depression.

List of publications

Paper I:

Kjelby E, Jørgensen HA, Kroken RA, Løberg EM, Johnsen E (2011): **Anti-depressive effectiveness of olanzapine, quetiapine, risperidone and ziprasidone: a pragmatic, randomized trial.** BMC Psychiatry, 2011 Aug 31; 11:145, doi: 10.1186/1471-244X-11-145.

Paper II:

Kjelby E, Gjestad R, Sinkeviciute I, Kroken RA, Løberg, E-M, Jørgensen HA, Johnsen E (2018): **Trajectories of depressive symptoms in the acute phase of psychosis: Implications for treatment.** J Psychiatr Res, 2018 Aug; 103; 219-228, doi: 10.1016/j.jpsychires.2018.06.003.

Paper III:

Kjelby E, Gjestad R, Løberg EM, Reitan SK, Joa I, Larsen TK, Rettenbacher M, Fathian F, Sinkeviciute I, Alisauskiene R, Anda LG, Berle JØ, Fasmer OB, Kroken RA, Johnsen E

Antidepressive effectiveness of amisulpride, aripiprazole and olanzapine: a pragmatic, randomized trial (ready to be submitted)

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Related publications not included in this thesis

Kjelby E, Sinkeviciute I, Gjestad R, Kroken RA, Løberg EM, Jørgensen HA, Hugdahl K, Johnsen E (2015): **Suicidality in schizophrenia spectrum disorders: The relationship to hallucinations and persecutory delusions.** Eur Psychiatry, 2015 Oct; 30 (7): 830-6, doi: 10.1016/j.eurpsy.2015.07.003

Abbreviations

5-HT	5-hydroxytryptamine (=serotonin)
AIC	Akaike Information Criterion
ANOVA	analysis of variance
APA	American Psychiatric Association
BAVQ	Beliefs about Voices Questionnaire
BeSt InTro	Bergen-Stavanger-Innsbruck-Trondheim study
BIC	Bayesian Information Criterion
BP	the Bergen Psychosis project
BPRG	Bergen Psychosis Research Group
BPRS	Brief Psychiatric Rating Scale
CAFE	Comparison of Atypicals in First Episode study
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CBT	cognitive-behavioural therapy
CDSS	Calgary Depression Scale for Schizophrenia
CGI-S	Clinical Global Impression – Severity scale
CI	confidence interval
CUtLASS	Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study
DDD	defined daily dose

DSM-IV	Diagnostic and Statistical Manual for Mental Disorders
DUP	Duration of Untreated Psychosis
ECT	electroconvulsive therapy
EPS	extra-pyramidal symptoms
EUFEST	European First-Episode Schizophrenia Trial
FDA	U.S. Food & Drug Administration
FEP	first-episode psychosis
FGA	first generation antipsychotic
GAF	Global Assessment of Functioning Scale – Split version
GAF-S	Global Assessment of Functioning Scale – Symptom subscale
GAF-F	Global Assessment of Functioning Scale – Functioning subscale
GMM	Growth Mixture Models
GCP	Good Clinical Practice
HAM-D	Hamilton Depression Rating Scale
ICD-10	International Statistical Classification of Diseases
ICH-GCP	International Conference on Harmonisation - Good Clinical Practice
IPS	Individual Placement and Support - supported employment
ITT	Intention-to-treat analysis
LGC/LGCM	Latent Growth Curve Models
LME	Linear Mixed Effects models

LOCF	Last Observation Carried Forward
MADRS	Montgomery-Åsberg Depression Rating Scale
MAR	missing at random
NORMENT	Norwegian Centre for Mental Disorders Research
OR	odds ratio
PANSS	the Positive and Negative Syndrome Scale for Schizophrenia
PORT	the Schizophrenia Patient Outcomes Research Team (PORT)
RANZCP	Royal Australian and New Zealand College of Psychiatrists
RBANS	the Repeatable Battery for the Assessment of Neuropsychological Status
RCT	randomized controlled trial
RMSEA	the Root Mean Square Error of Approximation
SCID-1	Structured Clinical Interview for DSM-IV Axis I disorders
SD	standard deviation
SEM	Structural Equation Modelling
SGA	second-generation antipsychotic
SIGN	Scottish Intercollegiate Guidelines Network
SOHO	the Schizophrenia Outpatient Health Outcome Study
SPSS	Statistical Package for the Social Sciences
SNRI	serotonin and noradrenaline reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor

TAU	Treatment as usual
UK	United Kingdom
UKU	Udvalg for Kliniske Undersøgelser, Side Effects Rating Scale
US	United States of America
WFSBP	World Federation of Societies of Biological Psychiatry
WHO	World Health Organization

Table of contents

1. Introduction

Depressive syndromes are important and often neglected parts of the greater puzzle of schizophrenia or the non-affective psychoses. Depression in the context of psychosis may be viewed in three principal settings; 1) accompanying schizophrenia or other non-affective psychosis, 2) as part of schizoaffective disorder or 3) in severe episodes of affective disorders. Initially though, depression needs to be illuminated in the greater context of the schizophrenia spectrum disorders before the depressive phenomena can be explored more profoundly:

1.1 Schizophrenia

Firstly the schizophrenia syndrome was described by Emil Kraepelin in 1887 as "dementia praecox" (1) and named "schizophrenia" by Eugen Bleuler in 1911 (2). The schizophrenia spectrum disorders encompass a diverse range of sometimes chronic symptoms like hallucinations, delusions, formal thought disorders, behavioural disturbances, functional impairment, neurocognitive symptoms and negative symptoms like avolition, anhedonia, alogia and affective flattening. Several experts advocate the view of schizophrenia as a neurodevelopmental disorder (3).

Schizophrenia is among the most devastating illnesses in the global health context, as demonstrated by its ranking in the World Health Organization as one of the top fifteen illnesses contributing to the global burden of disease (4). Among the psychiatric syndromes and disorders schizophrenia is only surpassed by Major depression on this list of disorders.

1.2 Schizophrenia-spectrum disorders or the non-affective psychoses

A classification based on operational criteria leading to more stable and reliable constructs of groups of disorders has been the primary strategy for classification of the psychiatric disorders from the DSM-III in 1980 forward (5). Reaching conclusive diagnostic conclusions in psychiatry is notoriously challenging and subject to continuing discussions, most recently the last decade when revisions of the DSM-IV (6) and the ICD-10 (7) have been under work. The DSM-V was published in May 2013 (8) and the first English version of the ICD-11 (9) was published in June 2018 and will come into effect on January 1st 2022. The diagnostic classification applied in the papers of this thesis is the ICD-10.

The grouping of the schizophrenia spectrum disorders vary in different publications and guidelines and is often imprecisely defined. While the following diagnoses (with ICD-10 diagnoses in parentheses) are almost invariably referred to as within the schizophrenia spectrum: schizophrenia (F20), schizoaffective disorder (F25) and schizophreniform disorder (F20.8), some are included less systematically: acute polymorphic psychotic disorder with symptoms of schizophrenia (F23.1), acute schizophrenia-like psychotic disorder (F23.2), other acute predominantly delusional psychotic disorders (F23.3), delusional disorder (F22) and schizotypal disorder (F21) (10, 11). Finally some diagnoses are even more irregularly included in the definitions of the spectrum: all acute and transient psychotic disorders (F23), other non-organic psychotic disorders (F28), unspecified non-organic psychosis (F29) and drug-induced psychosis (F1x.5) (8, 12, 13). “Schizophrenia and other psychotic disorders” in the DSM-IV (6) has been renamed “Schizophrenia Spectrum and Other Psychotic Disorders” in the DSM-V (8), while in the first published ICD-11 version (9) the term “schizophrenia spectrum” is not applied. Schizoaffective disorder (14) has been a particular focus of discussion due to its position in-between schizophrenia and affective disorders, but is still, despite the controversies, maintained in the DSM-V and ICD-11 classifications. The spectrum comprised by the ICD-10 diagnoses F20-

F29 is also referred to as the non-affective psychoses; psychotic disorders that are not part of unipolar major depression or bipolar disorder.

The Task Force responsible for recommendations to the DSM-V suggested 11 criteria for new categories, for instance common genetic factors, neural substrates and biomarkers (15). For the schizophrenia spectrum there is evidence from genetic studies of common factors, but also overlap with disorders of other categories, for instance bipolar disorder (13, 16).

A further complicating trait is the poor diagnostic stability of the schizophrenia spectrum. A systematic shift from unspecified subdivisions of psychoses (17) and substance-induced psychosis to schizophrenia has been documented (18). Although a temporal consistency in the diagnosis of schizophrenia and bipolar-I disorder has been found, some "diagnostic drift" both for first-episode psychosis (FEP) and in the long-term follow-up has been demonstrated between schizophrenia, schizoaffective disorder, acute psychoses, drug-induced psychoses and unipolar and bipolar depression with psychotic features (19, 20). Some findings indicate that there is a bias toward diagnosing major depression with psychotic symptoms in the face on uncertainty, until a diagnosis of schizophrenia is reconsidered and decided upon (21). Keller et al (22) reported difficulties in distinguishing between psychotic depression and schizoaffective disorder in the early episodes and even non-psychotic patients with a unipolar depressive episode have a high progression rate to schizophrenia (23). The episodic character of psychotic depression may in the long term help to distinguish this depression subtype from schizoaffective disorder where the latter tends to be chronic with a chronic thought disorder even when the patient is not depressed (22). This knowledge is however of little help in the debuting psychotic patient. Schizoaffective disorder is an unreliable diagnosis and has been shown in some studies to be more similar to affective disorders while in some resembling the course of schizophrenia (14, 24). Psychotic depression is a grossly understudied illness within the field of psychiatry in urgent need for more research (25). However, as this thesis has non-affective psychoses as its main focus, psychotic depression will

not be elaborated further, except for discussions of diagnostic uncertainty and sensitivity analyses in the BP.
Complicating a synopsis of the literature in the post-neuroleptic era are the changes in diagnostic criteria in the ICD and DSM revisions and different cultural diagnostic trends globally, for instance a propensity in the US in the 1960s and 1970s to diagnose manic-depressive illness as schizophrenia (26, 27). These diverse relationships complicate comparisons based on diagnostic subgrouping in research in the long-term perspective.

Therefore, there is a rationale for investigating the broader spectrum of psychoses. However, the rationale for investigating more homogeneous subgroups of disorders is also present as heterogeneity will contribute to difficulties in the interpretation of data. Subsequently this thesis investigates both a broader psychosis spectrum and the narrower schizophrenia spectrum. Moreover, I will also attempt to disentangle the heterogeneity of the widely defined diagnostic spectrum study cohorts in order to investigate the significance for more narrowly defined subgroups.

1.3 Treatment of Schizophrenia

Medical treatment of schizophrenia was revolutionized in the 1950s with Henri Laborit's discovery of the neuroleptic properties of chlorpromazine and subsequently Deniker and Delays reports of a marked effect of chlorpromazine monotherapy in psychotic patients (28, 29). Although the field of neuroscience has evolved tremendously the last decades, few of these advances have led to the launch of new treatments for schizophrenia yet. The effectiveness of medical treatment has not improved significantly since the development of clozapine in 1958 with the subsequent marketing in 1972 (30) and the highly important findings of a superior efficacy in treatment-refractory schizophrenia (31), although contemporary treatment of schizophrenia is more targeted with the second generation antipsychotic drugs (SGAs). The SGAs were developed based on the observation that clozapine was

highly effective for psychotic symptoms and had a substantially lower propensity to cause extrapyramidal side-effects (EPS), an observation leading to the descriptive term “atypical antipsychotics” being applied to this new class of antipsychotics. Some of the atypical traits have been attributed to the 5-HT_{2A} antagonism of the SGAs. Although some first generation antipsychotic drugs (FGAs) are also potent 5-HT_{2A} antagonists, the SGAs are characterized by greater affinity for the 5-HT_{2A} receptor than for the D_2 receptor (32). The term SGAs will be applied in this thesis synonymously with atypical antipsychotics, although there may be some minor differences in the demarcations of these terms. Amisulpride, contrary to its lack of affinity for the 5-HT_{2A} receptor, but due to its atypical efficacy profile (33, 34), will be included with the SGAs in this thesis. Overall SGAs are observed to cause less side-effects than FGAs, however with large differences between individual SGAs (35). The assumed overall superiority of SGAs vs. FGAs regarding side-effects has been subject to debate (36) and some even suggest to abandon the terms FGAs and SGAs (37). The selection of available pharmacologically differing antipsychotics is greater than ever, thus facilitating more individualized medication choices based on side-effects profiles and the preferred formulation of administration. Moreover, the steadily increasing availability of different long acting formulations (LAIs) of antipsychotics strengthen continuity in treatment, counteract antipsychotic non-adherence and prevent relapses (38). The evidence for the strengths of LAIs comes from observational and mirror-image studies rather than from RCTs (38). Consequently, this extensive panorama of antipsychotic drugs and formulations may contribute to improved adherence and relapse prevention. Furthermore, the treatment is more integrated with contributions from evidence-based psychosocial treatments, particularly Cognitive Behaviour Therapy (CBT) (39), family interventions (40), improved social care, strengthened work and societal function with documented effective interventions like IPS (Individual Placement and Support) and Supported Employment (41, 42), Intensive Case Management (43), exercise therapy programs (44), music therapy (45), social skills training (46), cognitive enhancement programs (47) and treatment of co-existing somatic disorders, the latter of which is of utmost

importance considering the 15 to 20 year shorter life span of individuals with schizophrenia (48). Early-detection programs to reduce duration of untreated psychosis (DUP) have also documented improved short-term and long-term outcomes (49, 50), however not in all cohorts (51). Individualized inpatient milieu-therapy with optimized ward atmosphere based on inpatient symptom and function characteristics is still an important part of holistic hospital treatment (52).

The discovery of the FGAs and the unravelling of their pharmacodynamic profiles led to an increasing insight in the pathophysiology of the psychotic disorders. The biological basis for the development of schizophrenia-symptoms is seen as an evolving complex interplay of minor neurodevelopmental disruptions, non-specific behavioural disturbances in the adolescent prodrome co-occuring with the processes of synaptic pruning, CNS-differentiation and myelination (53) and then culminating in definite psychotic symptoms. The dopamine theory is the leading framework for understanding the emergence of psychotic symptoms. This theory is supported by the known pharmacodynamic properties of antipsychotics and the psychosis-inducing properties of pro-dopaminergic substances like amphetamines (54). The dopamine theory has been further elaborated in form of the aberrant salience theory of hyperdopaminergia for emerging psychotic symptoms (55) and eventually more recent evidence from PET-studies of distinct presynaptic dopamine synthesis-abnormalities (56). The underlying cause for the presynaptic dopamine dysfunction is however not determined, although prefrontal dysfunctions (57) or glutamatergic disturbances (58) have been hypothesized as potentially influencing factors and supported by emerging evidence (59).

1.4 Depression in Schizophrenia

Depression remains, despite improved and integrated treatment of schizophrenia, a major cause of suffering and impaired functioning in schizophrenia spectrum disorders. The modal rate of depression is estimated at around 25%, with measures ranging vastly from 7% to 75% (60). This large variation in prevalence may be caused

by different definitions of depressive symptoms and of the depressive syndrome, application of diverging psychometric scales and substantially different samples. In addition, depression is more prevalent in some phases of the disorder (60, 61), which is further elaborated in the next sub-chapter. The identification of depression in this patient group is challenging for several reasons, for instance due to the overlap between depressive symptoms, extrapyramidal – dysphoria resembling - side-effects of antipsychotic treatment and the negative symptoms of psychosis (61-63), a topic investigated in more depth in following sub-chapters.

Although some reports have suggested that depressive symptoms in schizophrenia are associated with a more favourable course (64-67), depression has for the most part been shown to be associated with a poorer quality of life (68-70), worse functioning (71, 72), longer duration of hospitalizations (73), increased rates of relapse (74-76), reduced rate of remission and recovery (71, 77) and suicide (12, 78).

Depressive symptoms may be viewed as a separate dimension of psychopathology in schizophrenia, similar to positive and negative symptom clusters (79). Factor analyses examining rating instruments, like the Positive and Negative Syndrome Scale (PANSS) (80), repeatedly conclude with a depression dimension in addition to a positive and a negative dimension, overall five factors also encompassing an excitement/agitation and a disorganized symptom dimension (81-83). Recently, arguments for understanding depressive symptoms not just as comorbid phenomena, but as independent components of schizophrenia have been summarized, with an emphasis on the preponderance of depressive symptoms in the prodrome and early-phase schizophrenia (84). The aetiopathological importance of determining if the depressive symptoms are co-syndromal to – coexistent with - schizophrenia or if depression is a separate condition – a “real” comorbid phenomenon - have been discussed (85). Both models may be valid, however the distinction may have potential implications for in which circumstances treatment with antidepressants may be effective. Birchwood et al. (86) argued for three different pathways to depression in schizophrenia; depression as an integral part of the illness itself, as a psychological

reaction to the illness and as a consequence of disturbed developmental pathways due to trauma.

1.4.1 Subtypes of depression in the temporal relation to psychotic episodes

The phenomenology of depression in schizophrenia is complex, both regarding the relation to phase of illness and the causes of depressive symptoms and depression-like behaviours (87, 88). Some of the different aetiological relationships will be described in this paragraph while some (e.g. EPS and pro-depressive medications) in other sub-chapters. Concerning the temporal aspects, depressive symptoms can be categorized according to their presence in different phases of the disorder:

Depressive symptoms are prevalent in the prodromal phase and during a relapse, often preceding positive and negative symptoms and the initiation of antipsychotic medication (76, 89, 90). Depressive symptoms are also frequently occurring (17-83%) during the first episode of schizophrenia (21, 78, 90-94). The widely varying estimates are probably due to heterogeneity in the study populations, differences in assessment tools and whether the depressive affect, the symptom or the depressive syndrome, is assessed (60).

Moreover, depressive symptoms are frequent features preceding psychosis and accompanying episodes in about half of the patients (11, 72, 95-99). Schennach et al (11) in acutely ill patients with schizophrenia spectrum disorders found depressed mood in 80% and a depressive episode in 39% at admission. Green et al (98) found that the onset of depression was concurrent with the onset of psychosis to a highly disproportionate degree compared to the overall time spent in acute psychosis relatively to stable, prodromal and post-psychotic periods. Depressive symptoms in an acute episode are known to decrease as the positive psychotic symptoms are successfully treated (61, 91, 99-102).

Table 1 Diagnostic criteria post-psychotic depression & schizoaffective disorder

	Post-schizophrenic depression (ICD-10)	**Schizoaffective disorder** (ICD-10)	**Schizoaffective disorder** (DSM-IV)
Depressive symptoms	A depressive episode, which may be prolonged, arising in the aftermath of a schizophrenic illness. The depressive symptoms are prominent and distressing, fulfilling at least criteria for depressive episode and have been present for at least 2 weeks.	Episodic disorder where both affective and schizophrenic symptoms are prominent during the same episode and concurrently for at least some time of the episode, but do not meet criteria of either schizophrenia or depressive or manic episodes	Uninterrupted period of illness during which there is a major mood episode concurrent with symptoms that meet criterion A for schizophrenia (hallucinations, delusions, disorganized speech, catatonia, negative symptoms). Manic or major depressive symptoms must be present for a substantial portion of the total duration of the illness. The depressive episode must include depressed mood.
Relationship to psychotic symptoms	The general criteria for schizophrenia have been met within the past 12 months, but are not met at the present time. Some schizophrenic symptoms, either "positive" or "negative", must still be present but they no longer dominate the clinical picture.	Within the same episode, at least one typical schizophrenic symptom: Formal thought disorder, delusions of control, hallucinatory voices, bizarre delusions etc., should be present for most of the time during a period of ≥2 weeks.	Psychotic symptoms must also be present in the absence of major mood symptoms, for a period of at least 2 weeks.
Exclusion criteria	If the patient no longer has any schizophrenic symptoms, a depressive episode should be diagnosed If schizophrenic symptoms are still florid and prominent, the diagnosis should remain that of the appropriate schizophrenic subtype	The disorder is not attributable to organic brain disease or to a psychoactive substance. Other conditions in which affective symptoms are superimposed on a pre-existing schizophrenic illness, or co-exist or alternate with persistent delusional disorders of other kinds, are classified under F20-F29 Mood-incongruent psychotic symptoms in affective disorders do not justify a diagnosis of schizoaffective disorder.	The disturbance is not due to the effects of a substance or a general medical condition.

Based on American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Arlington, VA, 2000 and World Health Organization,
International Statistical Classification of Diseases and Related Health Problems, 10th Revision, 1997.

Depressive symptoms are also prevalent in the post-psychotic phase which in ICD-10 is defined as the first year after a psychotic episode within schizophrenia (6, 7). Post-psychotic depression was first described as a reaction to the psychotic episode by Mayer-Gross in 1920 (103) and more thoroughly described by McGlashan and Carpenter in 1976 (67, 104), which lead to a renewed research interest. The concept

and definition of post-psychotic depression has been challenged and thoroughly discussed with misdiagnosis and a relation to potential pro-depressive aspects of FGAs being among the debated views (62, 105-111). The history of the discovery of PPD and the prolonged still ongoing debate about its phenomenological validity and contextual delineation, is summarized in more depth in a paper by Jeczmien (112). PPD is a separate diagnosis (F20.4) in the ICD-10 disease classification system (7) (Table 1). In the DSM-IV PPD is included in the appendix, but not diagnosed separately (6). PPD is not included in the DSM-V nor in the ICD-11, however depressive symptoms are included as a dimension score or as a symptom sub-specification (8, 9, 113). The 12 months limitation in the ICD-10 post-psychotic depression criteria has been criticized as the diagnosis of PPD is frequently missed by the ICD-10 and due to indications that PPD was not more frequent the year after a psychotic episode than in the later stable phase (106). An alternative definition of PPD has been formulated by Birchwood et al (114), namely that PPD occurs following the remission of acute psychosis, where the individual shows «at least moderate depression», does not show a concomitant increase in psychotic symptoms and is preceded by a subthreshold (non-depressed) phase. In a 10 year follow up of acutely psychotic patients in an early intervention study 28% were scored as depressed at 1 year, 20% at 2 years, 16% at 5 years and 19% at 10 years of follow up (72). Dollfus and Lancon (95, 96) found depression in 15% and 38% of stable patients with schizophrenia, respectively. Depressive symptoms following a psychotic episode can in principle be viewed as a) emerging *de novo* after a psychotic episode (67, 115, 116) or b) being revealed as depressive symptoms are overshadowed by positive symptoms in the acute phase (117). It has been hypothesized that post-psychotic depression might represent an already existing symptom complex that remits more slowly than the acute psychosis, contributing to such a symptom revelation (104). In the diagnostic guidelines of the ICD-10 of post-psychotic depression it is stated that “it is uncertain and immaterial to the diagnosis to what extent the depressive symptoms were merely uncovered by the resolution of earlier psychotic symptoms rather than being a new development or to what extent they were

an intrinsic part of schizophrenia rather than a psychological reaction to it" (61, 85). However, this is not uniformly agreed upon: Several researchers have investigated and found evidence that post-psychotic phenomena after both first and multiple episodes to some extent are part of a psychological reaction to the psychotic episode, particularly linked to appraisals of greater loss, humiliation, entrapment, shame and self-blame (86, 118) and that these aetiological considerations are vital to the planning of psychological treatment. A small UK study interviewed post-psychotic depressed FEP-patients with a qualitative method and proposed a model of depression where the following themes emerged as relevant: Coming to terms with the psychotic episode, blaming the medication, embarrassment at actions taken whilst unwell, fear of relapse, losing purpose in life, feeling misunderstood and ignored, social withdrawal and wanting to get better, contributing to feelings of shame, hopelessness, loss, entrapment, isolation and suicidal ideation (88). Arguments against the extensive focus on post-psychotic depression have been made on the basis that depression occurs in all phases of the illness (79, 106).

Concerning symptomatic characteristics and phenomenology of depressive symptoms in schizophrenia Becker et al. (119) found a symptom complex in secondary depression in schizophrenia which was separable from primary depression, whereas Weissman et al. (120) could not detect differences in the pattern of depressive symptoms.

Demoralization is a condition with several similarities to depression in schizophrenia (73, 79). Chronic demoralization is however not a concept exclusive for schizophrenia, and has been observed to occur in depression, cancer and other medical and psychiatric illnesses (121). Demoralization is seen as a syndrome of existential distress particularly frequently observed in illnesses that threaten life or integrity of being (121). Demoralization has been described in schizophrenia as a state of chronic and persistent hopelessness and low self-esteem in the absence of vegetative features of depression, often associated with an increased awareness of the illness and the consequences of the illness for achieving goals in life (122).

Demoralization is closely linked to hopelessness and suicide (79). On a more optimistic note, demoralization may be more amenable to psychotherapeutic intervention, thus reducing suicide risk (73, 123).

Paper 2 of his thesis aims to strengthen knowledge about the complexity of these depressive phenomena and the relation in time to psychotic episodes, in order to contribute to a more robust basis for the intervention for depressive symptoms in or after a psychotic episode.

Table 2: Receptor affinities

Receptor	amisulpride	aripiprazole	olanzapine	quetiapine	risperidone	ziprasidone
D_1	-	+	++	+	+	+
D_2	+++	++++	++	+	+++	+++
D_3	+++	++++	++	+	+++	+++
D_4	-	++	++	++	+++	++
5-HT_{1A}	-	+++	-	+	+	+++
5-HT_{2A}	-	+++	+++	++	++++	++++
5-HT_{2C}	-	+	++	-	++	++
α_1	-	++	++	+++	++++	++
α_2	-	-	+	-	++	-
H_1	-	-	+++	++	++	++
M_1	-	-	+++	+	-	-

Adapted from Abi-Dargham A, Laruelle M. Mechanisms of action of second generation antipsychotic drugs in schizophrenia: insights from brain imaging studies. European Psychiatry. 2005;20(1):15–27.

1.4.2 Antidepressive or dysphoria-inducing properties of antipsychotics?

In earlier psychoanalytic theory depression was seen as a perhaps obligate, natural transition in the improvement process of the psychotic syndrome (124). Moreover, in early descriptions by Bleuler (2), a reactive depression usually encountered at the onset and a schizophrenic melancholia, a depression which "somehow must stem from the disease process itself", was observed. A different perspective on this post-psychotic depression was the reports from antipsychotic drug trials of FGAs in the

1970s and 1980s which indicated depressiogenic side-effects of the FGAs (67, 125). A possible mechanism for such a pro-depressive pathway is the effects of FGAs on the cerebral reward and motivational system, as the mesocorticolimbic reward system is highly dependent on dopaminergic function (126). Indeed, viewed from their shared dopamine-antagonistic, particularly D_2-blocking abilities and thus antagonistic effects on the reward system, antipsychotics have been shown to induce dysphoria and depressive symptoms (127, 128). In a landmark study by van Putten et al (62) the depressiogenic effect only appeared in patients with antipsychotic-induced akinesia and was reversed in all akinetic patients when the akinesia was successfully treated. The topic was subject to debate (129, 130). A record-based long-term retrospective observational study investigating depressive symptoms in florid psychotic phases of chronic schizophrenia in the pre-neuroleptic vs. early-neuroleptic era, found that the bulk of patients with depressive symptoms were found in the pre-neuroleptic intervals and that patients who never developed depression had been exposed to psychotropic drugs for the same length of time as the depressed group (131). Several studies of acute psychotic patients and long-term follow-up cohort studies indicated that depression was integral to the schizophrenia disorder and that pharmacogenic, antipsychotic-induced depression although sometimes occurring, was not the main cause for depression in schizophrenia (99, 132, 133) and indeed that acute-phase and long-term neuroleptic treatment was associated with a reduced risk of depression or dysphoria (117, 134, 135). Findings concerning the contribution of high-dosage antipsychotic treatment to possible drug-induced depressive symptoms are equivocal, although most studies from the last decades show no association between high dosage and depression (62, 133, 134, 136-138). There is a growing evidence base not supporting a depression-inducing effect of antipsychotics on a group level in both FEP and stabilized cohorts (71, 92, 99, 117, 131, 133, 138-141).

Voruganti and Awad (142) postulated a new model for neuroleptic dysphoria with a synthesis bases on a review of clinical research supplemented with neuroimaging findings and novel concepts concluding with less neuroleptic dysphoria with atypical antipsychotics. Moreover, SGAs may not to the same degree as FGAs block the

dopaminergic reward system, possibly contributing to a smaller dysphoric risk with SGAs (143).

Contrasting the dysphoric properties, several studies of antipsychotic medication for different psychiatric disorders have actually indicated antidepressive properties for several SGAs (144, 145). Different hypotheses have been postulated with regard to which mechanisms underlie the antidepressive effects of the SGAs, including antagonism of serotonergic 5-HT_2-receptors, agonism of 5-HT_1-receptors and antagonism of adrenergic α_2-receptors of which several properties (Table 2) are inherent to the study drugs of this thesis (32, 34, 146). Inhibition of trans-membrane monoamine transporters, resulting in increased level of serotonin and/or norepinephrine, a pharmacodynamic process similar to that of antidepressants, has been demonstrated not only for some SGAs (ziprasidone, zotepine and quetiapine), but also for a few FGAs (chlorpromazine and chlorprotixene) (147-150). In a receptor-imaging-review 5-HT_{2A} occupancy rates were found to be associated with favourable treatment outcomes for depressive symptoms and improvement of cognitive function within schizophrenia (151). Amisulpride, which is among the most efficacious SGAs (35, 152), is an interesting compound pharmacodynamically with regards to the hypothesised mechanisms of its anti-depressive effect, as amisulpride seems to have anti-depressive properties, despite no affinity for 5-HT receptors. A differential effect on topographically different parts of the dopamine system is one possible explanation (32, 33). Inflammation has been postulated as contributing to affective symptoms and as a possible target for anti-depressive effects for some antipsychotics (153), however some publications do not find associations between inflammation and depression in schizophrenia (154).

Some researchers have hypothesized that genetic polymorphisms related to dopaminergic and serotoninergic neurotransmission might affect antidepressive efficacy of SGAs (155) and some found that depressive symptoms in neuroleptic-naive first-admission schizophrenia patients are associated with low presynaptic dopamine function, a proposed model that may have implications for drug-treatment, e.g. in prediction of response to D_2 receptor blocking antipsychotic drugs (156). This

finding corresponds with leading research on treatment resistant schizophrenia where results suggest that treatment resistance is coupled with a lack of elevation in striatal dopamine synthesis capacity, thus hypothetically explaining the lack of effect of dopamine-blocking antipsychotics (157).

1.4.3 The relationship to negative symptoms and extra-pyramidal side-effects

Negative symptoms:

Negative symptoms of schizophrenia are conceptualized as an absence or reduction of normal processes and behaviours and largely replaced the term defect or deficit symptoms in the 1970s (158), although the term negative symptoms was first used by Hughlings Jackson as early as in 1887 (159). Sub-symptoms within the negative syndrome include avolition/apathy, anhedonia, asociality, blunted affect and alogia (160). In addition, negative symptoms are subdivided into primary (core feature of the schizophrenia illness) vs. secondary (due to extrinsic causes like depression, side-effects and organic pathology) (79, 161). Viewing depression in the context of negative symptoms, there is a substantial behavioural overlap between some aspects of the symptom clusters, for instance loss of motivation, blunted affect, anhedonia, sleep disturbances, lack of appetite, concentration difficulties, poverty of thought and speech and withdrawal from activities (asociality) (73, 162). These overlapping areas may be difficult to disentangle and may lead to difficulties in correct representations of symptoms and observations. Attempts have been made to measure characteristics discriminating depression from negative symptoms as for instance depressive mood, feelings of guilt, lack of self-confidence and suicide attempts (89, 97, 163). Thus, the Calgary Depression Scale for Schizophrenia (CDSS) which is the best validated instrument to discriminately measure depressive symptoms in schizophrenia, was developed (164). The development and validation of the CDSS is more thoroughly described in the “Assessment of depression” paragraph. There seems to be less overlap between cognitive depressive symptoms and vegetative depressive symptoms with negative symptomatology (165, 166). Although several studies identify

significant associations between negative and depressive symptoms cross-sectionally or prospectively (63, 65, 82, 91, 162, 167-169), a growing number of publications demonstrate the ability to measure depressive and negative symptoms discriminatively without a significant overlap (82, 91, 133, 170-172).

Interpreting results of treatment of negative symptoms and depressive symptoms, respectively, are influenced by the same uncertainty. In systematic reviews and meta-analyses of antidepressants for primary negative symptoms analyses were conducted to determine if significant effects might be confounded as a secondary consequence due to a primary effect on depressive symptoms (173, 174) .

EPS:

All antipsychotics may lead to extrapyramidal side-effects in the form of parkinsonism, dystonia and akathisia, however with large variations between drugs (35, 175). Parkinsonism causes motor retardation which may be confused with depressive symptoms and complicate diagnosis and treatment decisions. In an early paper by van Putten et al (62) the term “akinetic depression” in schizophrenia was coined, describing a depressive-like condition secondary to akinetic side-effects of antipsychotics that could be improved with successful treatment of the akinesia. Several subsequent papers have reported significant - though in some instances modest - correlations between EPS and dysphoria or depression (93, 167, 172, 176), Some find that treating EPS lead to resolution of depression only in some patients (117) and that depression may resolve even though EPS are not targeted (177). Some studies do not find significant associations between EPS and depression (91). In a long-term study of 364 outpatients, EPS and depressive symptoms were significantly positively associated (178). In a large placebo controlled trial of olanzapine and haloperidol (179) and one trial with quetiapine vs. haloperidol (180) the authors by means of path analyses concluded that there was a direct anti-depressive effect of antipsychotics on depressive symptoms. The indirect effect on secondary depressive symptoms through reduction in EPS could only to a minor degree explain the reduction in depressive symptoms. Dollfus et al (181) found that objective EPS were

strongly correlated with negative and depressive symptoms while subjective EPS were not. Akathisia, which presents as motor restlessness with a compelling urge to move and an inability to sit still, is one of the most common EPS occurring during antipsychotic treatment and may also emerge during treatment with antidepressants (182). Akathisia is known to be associated with dysphoria, suicide risk and depression, may contribute to difficulties in diagnostic conclusions between agitated depression and side effects of antipsychotic treatment and is often treatable with a change of antipsychotic medication or lowering dose or supplementary medication with beta blockers or benzodiazepines (128, 183) or mirtazapine (184).

1.4.4 Factors associated with depression

Studies primarily investigating factors linked to depression in schizophrenia are rare. Still, characteristics of schizophrenia patients with depressive symptoms have been investigated as secondary aims in a number of studies varying in illness duration and phase of illness. The cross-sectional nature of the vast majority of data precludes interpretation of cause and effect. Weissman et al (120) with regards to demographics and characteristics detected no differences between depressed and non-depressed patients with schizophrenia. However, some researchers identified characteristics:

Concerning sociodemographic characteristics conflicting results have been disclosed; some found better premorbid social function in depressed individuals, for instance that depressed patients were more often married and less often unemployed (61, 74, 91, 185) and had completed more education (186), while some found that depressed patients more often lived alone (138), were characterized by longer duration of untreated psychosis (DUP) (186), with worse social and occupational function (187), less family and social support and social isolation (188) and had a more chronic course of illness (74). Schizophrenia patients have reported depression as a main reason for substance use (189) and substance and alcohol abusing individuals have been found to be depressed more frequently (72, 79, 190, 191).

Insight into mental status has been found to associate with depression and hopelessness (192-195). Depressed or formerly depressed patients have reported more subjective experiences of psychological deficits of schizophrenia, a view of the illness as being chronic and disabling and during depression experiencing appraisals of loss, humiliation, entrapment, shame and self-blame (192, 196-199). The applicability of this knowledge as a basis for stigma-reducing interventions in treatment and the diagnostic process has been highlighted (200).

It is undetermined if somatic illness which is well known to contribute to major depression, has the same propensity to induce depressive symptoms in schizophrenia (201), although should be systematically screened for in the differential diagnostic process.

Depression has been linked to stressful life events in schizophrenia (138, 202) and to early trauma and childhood maltreatment (203, 204), indeed with depression/anxiety and unhelpful metacognitive beliefs mediating the relationship between early emotional abuse and positive psychotic symptoms (205). Poor premorbid childhood adjustment has been found to correlate with depressive symptoms in FEP (72, 94). A US study of schizophrenia found that Caucasians were seven times more likely to be diagnosed with a depression than African-Americans, which was not a definite observation that depression was more frequent in Caucasians, however that erroneous diagnostic conclusions could be a possible explanation (185). Perceived discrimination among immigrants has been found to correlate with depressive symptoms in schizophrenia (206).

Regarding gender, most studies have found no differences in depressive symptom prevalence in men and women with schizophrenia (91, 93, 207). For comparison unipolar depression is about twice as frequent in women (208) while for bipolar disorder gender differences in the frequency of depression are small (209). One schizophrenia study found that alcohol was an associated factor for depression in men and symptoms of agitation/excitement in women (94).

Concerning genetic risk and family history, depression in schizophrenia has been found to be associated with a family history of unipolar or bipolar depression and an increased risk of developing depression in neuroleptic-treated patients with a family history of depression (91, 210, 211), however not in all samples (212).

Concerning age, a large cohort of first admitted schizophrenia patients and a small cohort of post-psychotic depressed vs. non-depressed patients found that depression was associated with older age (91, 212), although other FEP-cohorts found no associations with age (93). In older and often more chronically ill individuals with schizophrenia, depressive symptoms were found frequently (HAM-D ≥ 17: men: 7%, women: 20%, and mild symptoms in 60-63%) in schizophrenia patients who were included on the account of absence of a major depressive episode or diagnosis of schizoaffective disorder (213). A cross-sectional study of persons with schizophrenia >55 years detected clinical depression in 32%. Depression was associated with physical illness, quality of life, presence of positive symptoms, a smaller proportion of confidants in their social network, coping by using medications and coping with conflicts by keeping calm (214). Sub-syndromal depression was found in 29%.

Cross-sectional associations between positive psychotic symptoms and depression has been found in several studies (63, 93, 137, 170, 171, 186, 215) and associations between changes in positive and depressive symptoms have been reported (91, 100). In one study hallucinations, but not delusions were associated with depression (212). Auditory verbal hallucinations believed to be malevolent have been found to provoke negative emotions (anger, fear, depression, anxiety) and thus were resisted, while voices perceived as benevolent were greeted (216, 217). Another trial found negative affective responses, primarily depressive, in all patients with voices, independently of perceiving the voices as benevolent or malevolent (218). In a trial of metacognitive beliefs about voices and the relationship with depression, the metacognitive belief of perceived uncontrollability and danger of thinking proved to be a key variable in explaining differences in levels of depression and anxiety (219).

Concerning neurocognitive symptoms and their associations with depressive symptom in schizophrenia there are mixed findings with some finding negative associations (10, 220, 221), some no associations (222, 223) and some even positive associations with depressed FEP patients displaying better information processing speed (224).

Finally, vitamin D-deficiency has been linked to unipolar depression (225) and there is emerging evidence of an association with FEP as well (226).

1.4.5 Assessment of depression

A number of psychometric assessment tools have been applied in the measurement of depression and depressive symptoms in schizophrenia. Scales known from clinical studies of treatment of unipolar and bipolar depression have been used frequently, like the Hamilton Depression Rating Scale (HAM-D) (227), the Beck Depression Inventory (BDI) (228) and the Montgomery-Åsberg Depression Rating Scale (MADRS) (229). Moreover, subscales or factors identified in factor analyses of psychometric rating scales frequently applied in clinical studies of the treatment of psychosis, have been studied. These include varying depression factors or sub-dimensions of the PANSS (80, 81) and of the Brief Psychiatric Rating Scale (230). Overall however, these rating scales and sub-dimensions have shown insufficient capability in discriminating depressive symptoms particularly from negative symptoms and extra-pyramidal side-effects in "non-affective" psychotic disorders (62, 165, 166, 231, 232).

Calgary Depression Scale for Schizophrenia

Thus, Addington et al (164) endeavoured to develop a rating scale for depression in schizophrenia that possessed these discriminating capabilities, based on items selected from HAM-D (227) and the Present State Examination (233) on account of the results of a factor analysis, measures of internal consistency and face validity. The result was the Calgary Depression Scale for Schizophrenia which has been repeatedly validated in differing populations as a depression rating tool in schizophrenia, demonstrating

good construct validity (correlations with other depression rating scales and prediction of a major depressive episode), divergent validity (from positive, negative and extrapyramidal symptoms), predictive validity (level of depression predict outcome), internal reliability and inter-rater reliability, sensitivity to change and has been validated in adolescents and adults (164, 232, 234, 235). The scale was constructed to measure the level of core depressive symptoms in schizophrenia (236-238). International schizophrenia guidelines (128) and the Norwegian National guideline for the treatment of persons with psychotic disorders (239) preferentially recommend the CDSS in the assessment of depression. The CDSS consists of 9 items, each item rated from 0 to 3 points (0 = symptom absent, 1 = mild symptom, 2 = moderate, 3 = severe) resulting in a range of the CDSS sum score from 0 to 27. A CDSS sum score > 6 has a specificity of 82% and a sensitivity of 85% for predicting a major depressive episode (240). The scoring of the CDSS measures the preceding 2 weeks to the assessment point. Factor analysis of the CDSS have demonstrated 2 (depression and guilt) (241-243) or 3 (morning depression/early awakening in addition to the 2 aforementioned) factors (232, 237, 244). Some papers excluded item 7 (early awakening) as the item had small factor loadings, small correlations with the other items and removal of the item improved internal consistency (242, 243). Thus, there is some overlap between items of the CDSS, which is desirable with regards to the aspect of greater internal consistency of a test, but if too large may result in item-redundancy (245, 246), a duplication of content across items, which will be further considered in the discussion.

Clinically significant effectiveness differences in clinical trials are challenging to define. While in extremely large trials efficacy differences between treatments may be statistically significant, the magnitude of the difference may be so small that it is not clinically relevant or clinically significant (247). Establishing consensus with regard to the magnitude of depressive reduction and of differences in antidepressive effect between treatments that may be considered clinically significant, is complex. There are no established thresholds for response or remission of depression for the CDSS which is more clearly defined in Major depressive disorder (6, 7, 248-250). In Major

depression, the most frequently applied definition of response is a psychometrically derived reduction of symptoms to <50% from an initial level and remission is defined by a symptom reduction to a level below a given psychometric cut-off, for instance a score ≤10 on the MADRS-scale (249). One poster-abstract suggests a change in the CDSS sum score of 1.3 as a Minimum Important difference with an anchor-based and a distribution-based approach (251).

1.5 Treatment-studies of depression in schizophrenia

Some aspects of trials investigating the treatment of depressive symptoms of schizophrenia needs to be elaborated before the evidence regarding treatment can be further looked into.

1.5.1 Pragmatic trials and effectiveness trials

Traditional RCTs in psychiatry – also called efficacy trials – which aim to determine if a specific intervention is beneficial under ideal conditions, have several limitations: for instance age above an upper limit (often age >65 years) or the presence of common comorbidities like suicidal ideation and behaviours or drug or alcohol abuse leads to the exclusion of large groups of patients from the participation in such trials. So-called effectiveness trials have been conducted in schizophrenia research the last 15 years as a response to the resulting questionable generalizability of such short-term, often commercially funded trials with highly selected samples. Effectiveness trials are also frequently labelled “real-life”, “pragmatic” or “practical” trials. The common denominator for such trials is that both sample and trial environment should resemble daily clinical practice (252, 253). Effectiveness trials aim to determine if a treatment works under the usual conditions of care. Placebo is rarely the comparator in pragmatic trials. Effectiveness outcomes tend to be less detailed than the outcomes studied in smaller efficacy-oriented trials. Cochrane glossary defines Effectiveness as: “the extent to which a specific intervention, when used under ordinary circumstances, does what it is intended to do. Clinical trials that assess effectiveness are sometimes

called pragmatic or management trials." Efficacy is defined as: "The extent to which an intervention produces a beneficial result under ideal conditions. Clinical trials that assess efficacy are sometimes called explanatory trials and are restricted to participants who fully co-operate (254)." Study samples are larger and there are fewer exclusion criteria in pragmatic trials resulting in more representative samples (255, 256). For example, participants with substantial co-morbidities and serious, complicating features like substance-abuse and suicide-risk, may yet be included. The CATIE, EUFEST, CUtLASS and SOHO trials are examples of the pragmatic design (152, 257-259) and have inspired the designs of the BP and BeSt InTro studies. Several effectiveness trials are funded independently of the pharmaceutical industry, reducing the risk of funding bias. This is important as a review of head-to-head comparisons of SGAs found that outcomes were in favour of the funding company in 9 out of 10 studies (260) and conclusions in medical papers have been shown to be systematically more positive if funded by profit organisations even across medical disciplines (261). Other competing interests such as personal or academic, were not significantly associated with authors' conclusions. Thus, studies funded by non-profit organizations may conclude more independently.

1.5.2 Secondary outcome research

Most trials investigating the efficacy or effectiveness of different treatments for depressive symptoms in schizophrenia have, like the BP and BeSt InTro, been designed with psychotic symptoms as the primary outcome and thus have examined depressive symptoms as a secondary outcome (71, 262-264). Research on secondary outcomes may have several limitations: 1) sample biases e.g. the trials have been designed for the investigation of a different outcome and the inclusion thus based on the presentation of that outcome, possibly contributing to less pronounced expressions of secondary outcomes and less statistical power to detect effects on secondary outcomes 2) measurement issues e.g. the available secondary outcome measure may not be the desired one 3) research may be guided more by availability of data than research hypotheses 4) secondary outcomes may be more prone to missing data and 5)

aspects of the data collection may affect the generalizability to clinical populations (265-267). The implications for the findings in this thesis will be considered in the discussion.

1.6 Treatment of depression in schizophrenia

The evidence concerning treatment of depression in schizophrenia is limited and primarily derived from clinical trials of antidepressants for depressive symptoms in schizophrenia (268, 269). Regarding recommendations from guidelines only the recommendations specific for depression in schizophrenia spectrum will be referred to in this paragraph. Even meta-guidelines and guideline-reviews have been developed to help inform the readers in the chaotic abundance of guidelines (270-272). One of the most influential national guidelines, the National Institute for Health and Care Excellence (NICE) guideline, provide little help for clinicians as NICE define depressive symptoms in schizophrenia as outside the scope of the psychosis management guideline (273) and instead refers to the NICE depression management guideline, where depression in schizophrenia is not mentioned specifically (274). In common for most of the guidelines, pharmacologic treatment is the main focus, while psychosocial interventions receive less attention (271). Guidelines are unanimous in emphasizing the importance of detecting and monitoring depression. The importance of distinguishing core depressive symptoms that are not secondary to for instance negative symptoms or side-effects is also underlined in several guidelines; the American Psychiatric Association (APA), the World Federation of Societies of Biological Psychiatry (WFSBP), the Royal Australian and New Zealand College of Psychiatrists (RANZCP) and the Canadian, the Danish, the Swedish and the Norwegian guidelines (128, 239, 275-279). The utility and validity of applying the CDSS in this identification process is emphasized in several guidelines, among other the WFSBP, the RANZCP and the Canadian (128, 275, 278). Cognitive Behavioural Therapy (CBT) specifically for depression, particularly in the early phase or prodromal period, is recommended in the Italian guideline for early intervention

(280), the RANZCP (278), the Scottish Intercollegiate Guideline Network (SIGN) Management of schizophrenia guideline (281) and the Canadian schizophrenia guidelines (282). An expectant approach with depressive symptoms concurrent with an acute psychotic episode or relapse is generally recommended in the Japanese schizophrenia treatment algorithm, the APA-, the SIGN-, the WFSBP-, the RANZCP- and the German: the “Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde” (DGPPN) schizophrenia guidelines (116, 128, 278, 279, 281, 283, 284).

Treatment of depressive symptoms with antidepressants are recommended in most guidelines and meta-guidelines (128, 239, 270, 276-279, 283-285), although not in the Schizophrenia Patient Outcomes Research Team (PORT) guideline (286) which however, is not updated since 2010. The Scottish guidelines (281) state that individuals who meet the criteria for depressive disorder should be treated according to relevant clinical practice guidelines for depression, including the use of antidepressant medication. The guidelines suggest caution with the co-prescription of antidepressants due to possible interactions, increased side-effects and potential psychotic symptom exacerbation. The WFSBP-guideline and the Japanese algorithm recommend adjunctive treatment with lithium (128, 284). The APA and the WFSBP guidelines recommend electroconvulsive therapy (ECT) in specific circumstances, based on low-grade evidence (128, 279).

Regarding choice and dosing of antipsychotic medication several guidelines and consensus statements recommend SGAs to FGAs for depressive symptoms (128, 278, 279, 281, 285, 287, 288), although highlighting the scarcity of the evidence-base. Several review papers from experts within the field of depression in schizophrenia provide additional treatment recommendations, largely overlapping with the abovementioned (60, 78, 113, 116, 264, 289). Hausmann and Fleischhacker (73) proposed a treatment algorithm for depression in schizophrenia based on a review of the literature, incorporating systematically many of the mentioned interventions.

1.6.1 Effectiveness of antipsychotics

As mentioned earlier, a dysphoric effect of antipsychotics has been suspected (290), but studies find little evidence for a pro-depressive effect, even for FGAs (114, 135). In fact, several SGAs are approved for different affective disorders, for instance unipolar and bipolar depression (291-293). Quetiapine, lurasidone and an olanzapine-fluoxetine-combination are approved for treatment of bipolar depression by the FDA in the US (294). Moreover, some SGAs are approved for treatment-resistant non-psychotic depression: Aripiprazole (295), olanzapine (296), quetiapine (297) and risperidone (298) have proven superior to placebo as add-on treatment for non-psychotic depression refractory to treatment with antidepressants (299, 300).

Concerning antipsychotics in primary psychotic disorders; the weight of the evidence regarding the possible pro-depressive effect and the anti-depressive effect points to a predominantly antidepressant effect, as discussed earlier in the thesis. Short-term studies indicate antidepressive effects of several SGAs in non-affective psychosis, e.g.; olanzapine was superior to haloperidol in reducing depressive symptoms in a 6-week study (179), quetiapine was found to be superior to haloperidol in reducing depressive symptoms during an 8-week follow-up (180), Kasper et al (301) found quetiapine XR to be superior to risperidone at reducing depressive symptoms in patients with schizophrenia and amisulpride was found to be more effective for depressive symptoms than haloperidol and risperidone and equally effective to olanzapine (302-305). In some studies sponsored by the pharmaceutical industry quetiapine has demonstrated anti-depressive properties in both clinically depressed and non-depressed populations (306-308). A study by Mauri et al (102) that compared three typical compounds (fluphenazine decanoate, haloperidol decanoate, haloperidol) and five atypical agents (clozapine, olanzapine, quetiapine, risperidone and sulpiride) in a naturalistic setting, could not confirm that treatment with the SGAs as a class was more effective for depressive symptoms than FGAs, although there were significant improvements in depressive symptoms for several FGAs and SGAs. Aripiprazole was equally effective as ziprasidone for depressive symptoms in one study (309) and

superior to haloperidol in one trial (310). In an 8-week study of risperidone and haloperidol for depressive symptoms in FEP, the drugs were equally effective (71). A meta-analysis investigating negative symptoms as the primary outcome found as secondary outcomes that amisulpride and zotepine were superior to placebo for depression with small effect sizes (311).

However, a Cochrane-review of atypical antipsychotics for people with both schizophrenia and depression concluded that there were too few data to guide recommendations (312). The review has however not been updated since 2008 and only 3 studies were analysed. In a recent meta-analysis antipsychotics were superior to placebo for improvement of depressive symptoms, although the effect size was small (0.27) (33 studies, N=9658) (313). Castle and Bosanac (264) present an overview of trials of anti-depressive effects of SGAs until 2012, where the conclusion is that the most consistent effects are seen for quetiapine and olanzapine.
There are also indications that antipsychotic medication may have anti-suicidal properties (314), particularly pronounced for clozapine (315, 316).

The international Early Psychosis Association advocate in their "International clinical practice guidelines for early psychosis" the use of antipsychotics in the prodromal phase for patients with suicide risk or if depression has not responded to psychological treatment or treatment with antidepressants for 6 weeks. A similar recommendation applies for 5 years after the first-episode (317).

Available evidence from pragmatic studies indicate a general antidepressive effectiveness, however with few differences in effectiveness between the antipsychotics, exemplified with results from the CATIE (263) and the EUFEST trials (262). However, the CATIE publication reports a slightly superior antidepressive effectiveness for depressed patients randomized to quetiapine. The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) (258) was a pragmatic trial investigating the effectiveness of SGAs vs. FGAs as groups, and did not detect statistically significant differences in depression change between the groups of antipsychotics. The CUtLASS was not powered to investigate between-drug

differences. The 52 weeks Comparison of Atypicals in First Episode (CAFE) – study did not detect differences in antidepressive effectiveness in FEP between olanzapine, quetiapine and risperidone (318). A large German naturalistic observational study (319) did not find statistically significant differences in reduction of depressive symptoms between typical and atypical antipsychotics, however did not report between-drug differences. Additional findings from this trial were that SGAs were more frequently chosen for patients with higher depression scores and that more depressed patients often changed the antipsychotic medication. A 12-week naturalistic study found reduction in depressive symptoms, but no statistically significant differences between clozapine, olanzapine and risperidone (320). Olanzapine was found to be superior at 6, 12 and 24 months for depression vs. risperidone and haloperidol and at the 6 and 12 month time-points also superior to quetiapine in the Schizophrenia Outpatient Health Outcomes (SOHO) trial, a large industry-funded naturalistic observational study (321-323). Clozapine was non-inferior to olanzapine and both clozapine and olanzapine were superior to amisulpride, oral FGA and depot FGA antipsychotics for depressive symptom response at 12 months (321). A small, Italian naturalistic, observational study (324) found a significant reduction in depression for patients with a CDSS ≥ 5, however only comparing clozapine with SGAs.

In summary the efficacy - the effect in highly selected patient groups - is better documented than the pragmatic long-term effectiveness – the effect differences in less selected, more “real-world” representative settings - of SGAs for depressive symptoms in schizophrenia. Thus, there is a need for more pragmatic long-term trials comparing SGAs head-to-head.

1.6.2 Treatment with antidepressants

Concerning the evidence-base for antidepressants for depression in schizophrenia, the best investigated drug class is tricyclic antidepressants (TCAs). In descending order selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake

inhibitors (SNRIs) and α_2-blockers like mirtazapine have been studied. Even early reports on antidepressant treatment of post-psychotic depression indicated treatment failure (115). Two recent meta-analyses point to some efficacy of antidepressants for depressive symptoms in schizophrenia (268, 269). The most recent meta-analysis by Gregory et al (268) included 26 moderate to low quality trials and found a NNT of 5 in favour of antidepressant treatment regarding response (8 studies included), however non-significant improvement at end-point after sensitivity analyses (17 studies) including analyses for separate drugs and classes of antidepressants. Moreover, some reviews and meta-analyses fail to find robust and stable proof of efficacy for antidepressants (128, 325), including a not so recent Cochrane-review that was overall inconclusive (326). The Cochrane review identified only 11 studies that met the inclusion criteria, of which all were small and randomised fewer than 30 people to each group. For the outcome "No important clinical response" antidepressants were significantly better than placebo and the depression score at the end of the trial, as assessed by the Hamilton Rating Scale (HAM-D), suggested that using antidepressants was beneficial. A study of 365 patients which evaluated antidepressant add-on treatment within the acute treatment of schizophrenia spectrum disorder did not find a significant effect for depressive symptoms for neither remission nor response criteria (327). In summary, the evaluation of the evidence-base is consistently assessed as limited, based on few and small studies with methodological weaknesses.

Concerns about the risk of adjunctive antidepressant treatment to antipsychotics in schizophrenia have been raised regarding potentially worsened psychotic symptoms (328), QTc-prolongation (particularly for citalopram) (329) and drug-interactions with antipsychotics (128). The topic of antidepressant prescription in bipolar disorder, which might be a relevant comparison, is debated among other due to increased risk of switching to mania and doubt concerning the antidepressive efficacy (330). However, less is known about this risk in schizophrenia and schizoaffective disorder (145). Although recommendations still advice carefulness in the co-prescription of antidepressants in schizophrenia (128), reviews indicate that the combinations overall

can be accomplished with a low risk of exacerbation of psychosis and serious adverse effects (269, 331). Finally, there is some evidence that lithium may be effective for a subgroup of patients (128).

1.6.3 Non-pharmacologic treatment

Firstly, non-pharmacologic interventions will be accounted for in the context of the treatment of schizophrenia in general, then more focused treatment for depressive symptoms will be looked into. Treatment of psychosis has formerly incorporated psychoanalytic or psychodynamic treatment, where the psychoanalytic treatment in the Chestnut Lodge cohort was found largely not effective (332). No clear evidence was found for psychodynamic therapy in a Cochrane-review (333).

Cognitive behavioural therapy (CBT) (334) has largely replaced psychodynamic treatment in schizophrenia. The evidence for the efficacy of CBT in primary unipolar depressive disorders is extensive (335). CBT in the treatment of psychosis, has thus far mostly focused on positive psychotic symptoms; hallucinations and delusions (336, 337). Evidence for the effect of CBT for psychosis for depressive symptoms is starting to emerge, mostly as a secondary outcome (336-344).

Important supportive treatments in schizophrenia have to some degree investigated effects on depressive symptoms: psychoeducation was superior to standard care for depressive symptoms (345), although obviously intuitive, the effect of systematically improving the psychosocial situation of depresses indiviuals with schizophrenia is largely undocumented (264). Moreover, physical training/exercise therapy has been shown to improve depressive symptoms in schizophrenia (44, 346, 347).

Duration of untreated psychosis (DUP) has been suspected to be associated with depressive symptoms in FEP. If true, early intervention to reduce DUP may improve prognosis of depressive symptoms. Results are however scarce. A Finnish study comparing an early intervention program based on a need-adapted Family and Community orientated integrative Treatment Model vs. standard treatment showed a superiority of the active treatment for self-reported depression (348). In a meta-

analysis of early intervention vs. TAU, early intervention was superior to TAU for depressive symptoms at 6, 9 and 12 months, but not at 18 and 24 months. Effect sizes were small and smaller than for positive, negative and general symptoms (349). Integrated specialized early intervention has been shown to be more effective in a 1-year follow-up in Hong-Kong (350), but not in the Danish OPUS study with a longer follow-up (2 and 5 years) and more resources in the standard treatment (351).

The evidence-base for ECT for depression in schizophrenia is limited (352), despite ECT being thoroughly documented for unipolar and bipolar depression (353, 354). The evidence-base for ECT in schizophrenia mostly concerns the efficacy as pharmacotherapeutic augmentation, in catatonia or at high suicide-risk.

Reviews and meta-analyses of evidence-based psychosocial interventions for schizophrenia like assertive community treatment and intensive case management (43), supported employment (41), social skills training (46) and family intervention (40) have to a minor degree reported depressive symptoms as an outcome in schizophrenia, although with some promising results (355). In a Norwegian systematic review of supported employment and IPS where the majority of participants had severe mental disorders, there was no significant effect on depressive symptoms or quality of life (356).

1.7 Suicide and self-harm in schizophrenia spectrum disorders

Suicide attempts, self-harm and suicide are among the most serious challenges in the treatment of severe mental disorders. In schizophrenia it is estimated that about 5% of patients commit suicide (357) and that 20%-40% of patients attempt suicide (123). In the Danish national cohort schizophrenia had the highest absolute risk for suicide in women and the third highest in men among the mental disorders (358). Comorbid occurrence of unipolar affective disorder increased the cumulative incidence of suicide. Depressed mood, previous suicide attempts, hopelessness and fear of mental disintegration (12) are established as risk factors for suicide. Other risk factors

include younger age, early stage of illness, good premorbid adjustment or functioning, male gender, living alone, substance abuse, higher intelligence, access to lethal means, poor adherence to treatment and awareness of disease contributing to hopelessness (12, 359-362). However, the gender difference seems to be less marked among patients with schizophrenia than in the general population. Suicide rates in psychiatric admissions seen as a whole are highest during the first week of admission and the first week or month after discharge (363). In the year before first presentation to psychiatric services in FEP, suicide attempts occur frequently (in 10-20%) and are associated with depression and hopelessness (361, 364). Suicide attempt in the year before start of treatment was the strongest predictor of suicide in a 1 year follow-up after initiated treatment (365). Some studies find significant associations between violence and suicide threats or attempts (366, 367). Negative symptoms may have protective properties (368). Depression has been found systematically to predict increased suicide-risk. Hopelessness and suicidal thinking has been shown to follow depression in the period after remission of acute psychosis (114). Moreover, depression is particularly prevalent in the prodromal period and in the DUP phase and has been found to predict subsequent self-harm (369). A meta-analysis found that depressive symptoms in FEP were associated with greater odds of later suicidal behaviour in long-term follow-ups (1-30 year follow-up, median 24 months) (370). A substantial amount of the knowledge about suicide-risk is derived from registry-based studies, as few clinical trials and cohort studies are sufficiently powered to investigate suicide as outcome (371, 372). Very serious, however rare, self-mutilation like self-enucleation and amputation of the penis has been linked to schizophrenia with ongoing psychosis and the quality of psychosis and in some circumstances with comorbid depressive symptoms (373).

Regarding anti-suicidal treatment a recent national Taiwanese study indicated a dose dependent reduction of self-harm related hospital admissions with antipsychotic treatment (374). Clozapine has proven anti-suicidal properties (315, 375). Lithium, although shown effective for reducing suicide risk in bipolar disorder (376), is not at present proven effective for preventing suicide in schizophrenia, although sometimes

used for this indication, possibly due to the known antidepressive properties (128). In addition to clozapine, general preventive work on a community-level, treatment of depression, regular assessment of suicidality, prevention of akathisia, improvement of treatment-adherence, strengthening support, reducing substance-abuse and restricting access to lethal means are among recommendations in order to reduce risk of suicide attempts and suicide (128, 362). CBT has shown some early, promising results regarding reduction of suicidal ideation (377).

In summary, the literature about the course and quality of depressive symptoms in schizophrenia is comprehensive, but the results are varying. The treatment-recommendations for depressive symptoms in schizophrenia are few and founded on a weak evidence-base. Treatment with antidepressants have proven some but insufficient efficacy, and the antidepressive effectiveness of antipsychotics is subject to optimism. There is however a limited evidence base concerning potential differences in effectiveness between SGAs for this debilitating symptom area. Thus, there is a need to investigate effectiveness of SGAs head-to-head. Although courses and trajectories of depressive symptoms have been investigated in several trials, there is still limited knowledge about potential determinants of refractory depressive symptoms and predictors of response to treatment. Thus, there is a need to investigate depressive symptom-trajectories and predictors of anti-depressive response.

The literature-review of the introduction-section was finalized the 4th of November 2019.

2. Aims of the study

The overall aim of this thesis was, conducting pragmatic, randomized trials in patients with a current psychotic episode, to investigate the antidepressive effectiveness of second generation antipsychotics and to uncover and investigate trajectories of depressive symptoms.

More specifically we aimed:

1. To compare the antidepressive effectiveness between olanzapine, quetiapine, risperidone and ziprasidone (paper I).

2. To disentangle heterogeneity in the treatment response of depressive symptoms in patients suffering from acute phase psychosis by uncovering different trajectories of depressive symptoms (paper II).

3. To investigate possible predictors of the course of depressive symptoms, thus aiming to determine discriminating characteristics of patients with responding- vs. treatment resistant depressive symptoms (paper II).

4. To investigate whether significant differences in the antidepressive effectiveness between amisulpride, aripiprazole and olanzapine exist (paper III).

3. Methods

3.1 Research projects/setting

3.1.1 Recruiting centers

BP

Haukeland University hospital, Bergen (226 patients)

BeSt InTro

Haukeland University Hospital, Bergen (102 patients)
Medizinische Universität Innsbruck, Innsbruck (24 patients)
Stavanger University Hospital, Stavanger (13 patients)
St. Olav's University Hospital, Trondheim (5 patients)

3.2 Study population

Patients with a current psychotic episode with clinical indications for oral antipsychotic treatment were included in the studies.

3.2.1 Diagnostic process

BP

The inclusion was based on the presence of psychotic symptoms, as scored on the basis of a conducted SCI-PANSS-interview (378), irrespective of diagnostic group, thus reflecting the diagnostic uncertainty commonly present in the early treatment phases in acutely admitted psychotic patients who are nevertheless in need of antipsychotic medication. The diagnoses were obtained from the medical record at discharge.

BeSt InTro

The diagnoses were determined based on the Structured Clinical Interview for the DSM-IV (SCID-I) (6), which was conducted by the study personnel (psychologists, medical doctors or psychiatrists). In cases where diagnostic uncertainty remained, a diagnostic decision was reached as a consensus following a thorough discussion between at least two of the study doctors.

3.2.2 Inclusion and exclusion criteria

Inclusion criteria

BP

Patients (age ≥ 18 years) were eligible for the study if they

- were admitted to the psychiatric emergency ward for symptoms of psychosis as determined by a score of ≥ 4 on one or more of the items Delusions, Hallucinations, Grandiosity, Suspiciousness/Persecution or Unusual Thought Content on the Positive and Negative Syndrome Scale (PANSS) (80), a definition of ongoing psychosis applied in the TIPS early detection study (379, 380) and similar to the CAFE study (318)
- could cooperate with clinical assessments
- were candidates for oral antipsychotic drug therapy with one of the four first-line antipsychotics available in Norway at the time of the trial.

Current first-line SGAs at the time of the trial were risperidone, olanzapine, quetiapine and ziprasidone. The naturalistic design aimed to mimic clinical practice in which the antipsychotic treatment is initiated before the diagnosis is specified. Eligible patients eventually had to meet ICD-10 (7) diagnostic criteria for schizophrenia, schizoaffective disorder, acute and transient psychotic disorder, delusional disorder, drug-induced psychosis, bipolar disorder except manic psychosis and major depressive disorder with psychotic features.

BeSt InTro

Patients (age ≥ 18 years) were eligible for the study if they:

- had symptoms of psychosis compatible with a diagnosis within the schizophrenia spectrum according to ICD-10 diagnoses F20-29 (7) and DSM-IV (6)
- were characterized by the same definition of ongoing psychosis as in the BP (a score of at least 4 on one or more defining PANSS items (80)
- were considered candidates for oral antipsychotic drug treatment by their attending physician or psychiatrist

The diagnoses were as early as possible verified in a SCID-I interview. Participants where the diagnostic conclusion was not within the schizophrenia spectrum were excluded from the RCT. All patients were considered capable of providing informed consent and provided written informed consent before inclusion.

Exclusion criteria

BP

Patients were excluded from the study if they were unable to use oral antipsychotics, were suffering from manic psychosis, were unable to cooperate reliably during investigations, were candidates for electroconvulsive therapy, did not understand spoken Norwegian language, were suffering from an organic brain disorder - principally dementia - or were medicated with clozapine on admission.

BeSt InTro

Reasons for exclusion were inability to understand spoken Norwegian, organic psychosis due to limbic encephalitis detected by antibodies in serum, hypersensitivity to the active substances, pregnancy or participants who were breastfeeding. Additional exclusion criteria were the contraindications for the respective study drugs as summarized in the manuscript of paper 3.

3.2.3 Withdrawal criteria

Study withdrawal criteria included the patient's decision to withdraw from further follow-up, serious somatic events that indicated a different follow-up not in line with the protocol of the trials and pregnancy. In instances where intended concomitant use of more than one antipsychotic drug on a regular basis was found inevitable, the patient was excluded from the project. However, change of antipsychotic medication because of inadequate efficacy and/or side effects/safety issues was not a reason for disruption of the participation in the study. In line with the pragmatic design, information regarding reasons for change of medication and the choice of another agent is highly relevant information.

3.3 Study design

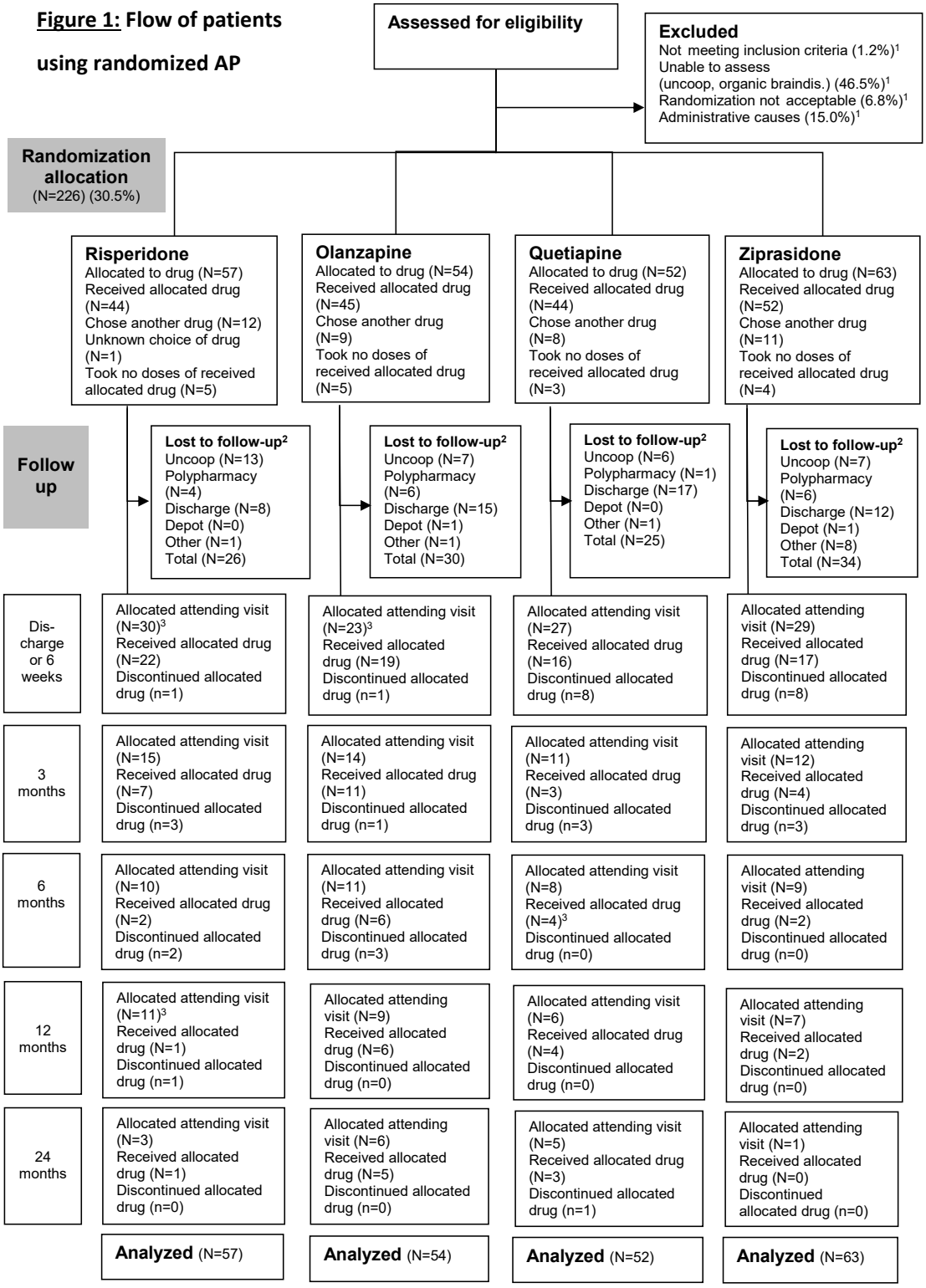
3.3.1 BP

The Bergen Psychosis Project (BP) is a 24-month, prospective and pragmatic antipsychotic drug trial (381). Patients were consecutively recruited between 2004 and 2009 from the Division of Psychiatry at Haukeland University Hospital in Bergen, Norway, with a catchment population of about 400,000. Assessments were at baseline, than at discharge or at 6 weeks if not discharged earlier, then at follow-up visits at 3, 6, 12 and 24 months (Figure 1: Flow-chart BP). Assessments were conducted by a rater blind to treatment. The main reason for drop-out between baseline and discharge was discharge from the hospital before one week had passed since baseline, which was defined as the minimum interval before the first follow-up assessment could be undertaken.

Randomization to a sequence was considered the preferred method. At admission, a sealed and numbered envelope was opened by the attending psychiatrist and then the patient was offered the first drug in a random sequence of olanzapine, quetiapine, risperidone or ziprasidone. The randomization was open to the treating psychiatrist or physician and to the patient. Both the treating clinician and/or the patient could

discard the SGA listed as number 1 on the list because of medical contraindications to or prior negative experiences with the drug. In that case the next drug on the list could be chosen. The same principle was followed throughout the sequence. A reason for discarding a drug was requested. In each sequence, the SGA listed as 1 defined the randomization group (RG). The actual SGA chosen, regardless of randomization group, defined the first-choice group (FCG). In the case that a patient already used an antipsychotic agent in therapeutic dosage at admission, no wash-out was required before starting the study drug. If a patient was randomized to the same agent already under use, the agent would simply be continued and dose adjustment made if indicated.

Figure 1: Flow of patients using randomized AP



Not meeting inclusion criteria = score below 4 on all the items: delusions, hallucinatory behaviour, grandiosity, suspiciousness/persecution or unusual thought content in the Positive and Negative Syndrome Scale (PANSS); Uncoop. = the patient was not able or willing to cooperate with testing and assessments; Organic braindis. = Organic brain disorder, principally dementia; Randomization not acceptable = patient or treating clinician not willing to change existing antipsychotic medication; Administrative causes = principally patient discharged before assessments could be made. AP (antipsychotic drug).

[1] enrolment started March 2003 until 2008, week 26. Full details on enrolment were only registered from 2006, week 31 until 2008, week 26. Consequently only percentages are displayed for patients assessed for eligibility and excluded patients

[2] before discharge/6 weeks - based on total randomized participants, irrespective of if the participant receiving the allocated drug

[3] some patients missed some follow-up visit, but were retested on later visits.

3.3.2 BeSt InTro

The BeSt InTro is a randomized, rater-blind head-to-head comparison of amisulpride, aripiprazole and olanzapine, with a one-year follow-up. Study-drugs were chosen with an intention to represent markedly different pharmacodynamic properties, elaborated in the introduction 1.4.2 (Table 2, p. 31) – exclusive dopaminergic properties for amisulpride (32), partial D_2-agonism for aripiprazole and a substantial 5-HT_{2A}-affinity for olanzapine (34, 146) - and to compare these pharmacologically different SGAs among which one SGA (olanzapine) has systematically proven to be the among the most effective in meta-analyses (35, 382). Thus, olanzapine was included in the trial design. Amisulpride has also been among the most effective in meta-analyses (35, 382). The decision to investigate these 3 antipsychotics in the BeSt InTro was primarily due to hypotheses regarding the primary outcome, antipsychotic effectiveness (Johnsen E et al, in press). However, the pharmacologic differences are also highly relevant with regards to antidepressive effectiveness (32). The participants were assessed at baseline, 1, 3 and 6 weeks, 3, 6, 9 and 12 months (flow-chart included in the paper 3-manuscript). Patients were consecutively recruited in a multi-centre cooperation lead from the Division of Psychiatry at Haukeland University Hospital in Bergen, including Stavanger University Hospital and St. Olav's University Hospital, Trondheim in Norway and the Medizinische Universität Innsbruck in Austria.

The randomization process and the criteria for the follow-up of the antipsychotic treatment were practically identical to the BP as described above and further

elaborated in paper 3. As in the BP the randomization was concealed from the research team involved in assessments and the first study drug in the sequence defined the randomization group, which the intention-to-treat analyses were based upon.

3.3.3 Drop-out/missing data

Drop-out and missing data are major challenges in all trials investigating treatment-effects in psychotic participants and may be associated with among other: trial-design, suboptimal medication effects, tolerability-issues and as inherent to the challenges of living with psychotic disorders (255, 380). Greater drop-out rates add to more uncertainty in findings (255, 383-385) and are difficult both to counteract and to adjust for. The anticipated substantial dropout rates of the BP and BeSt InTro were main reasons behind the choice of statistical method. Dropout limitations will be discussed in chapter 5.2.2.

3.4 Treatment

BP & BeSt InTro

The study medications used were oral tablets. Choice of antipsychotic dosage and further dosing, combination with other drugs or switching to another antipsychotic drug were left to the clinician's discretion. The BeSt InTro study, having a more stringent protocol than the BP emphasized that the study drug doses should be within the defined maximum dosage limits as set by the Summary of Product Characteristics. The dosage intervals were for amisulpride 50-1200 mg/day, aripiprazole 5-30 mg/day and olanzapine 2.5-20 mg/day and serum levels were measured at study visits in order to determine if effective concentrations were achieved and as a reflection of medication adherence. To resemble usual clinical practice, concomitant medications were permitted with the exception of additional antipsychotic drugs on a regular basis. This is in line with leading treatment guidelines which advocate antipsychotic monotherapy (273, 278, 279). The exception was cross-titration during antipsychotic

drug switches. In cases where intended concomitant use of more than one antipsychotic drug on a regular basis was inevitable, the patient was deemed non-eligible for the trial. At each visit, all medications were recorded and the mean antipsychotic drug doses were calculated. Antipsychotic drug doses for the accepted sporadic use of antipsychotics, other than the SGAs under investigation, were converted to chlorpromazine equivalent doses (386). In cases where chlorpromazine equivalent doses could not be found in the literature, doses were converted to defined daily doses (DDDs) as developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology (387). The basic definition of the DDD unit is the assumed average maintenance dose per day for a drug used for its main indication in adults.

3.5 Data and variables

BP & BeSt InTro

Investigators administered the SCI-PANSS (378), a semi-structured interview for psychotic symptoms, at all study visits. Eligibility with regards to the presence of positive psychotic symptoms above the predefined level on key PANSS items was assessed based on the baseline SCI-PANSS-interview. Symptoms of depression were assessed by means of the Calgary Depression Scale for Schizophrenia (CDSS) (164). The CDSS was conducted at all study visits as a separate semi-structured, goal-directed interview. Furthermore, the patients underwent assessments including the Clinical Drug and Alcohol Use Scales (CDUS/CAUS) (388) and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (389, 390). The Clinical Global Impression-Severity of Illness scale (CGI-S) (391) and Global Assessment of Functioning Split Version, Functions scale (GAF-F) (6) were conducted to assess the general symptom and functioning level. Side-effects were assessed with the UKU side effects scale (Udvalg for Kliniske Undersøkelser) (392). Sociodemographic information was collected 1) in order to compare the study

population to other relevant trials 2) as descriptives in sensitivity analyses 3) to elucidate aspects of the randomization groups in baseline comparisons 4) to compare depression-trajectory groups 5) as predictors in the predictor-model in paper two and 6) to compare subgroups with more (CDSS>6) or less (CDSS≤6) depressive symptoms in paper 3.

3.6 Statistics

In both the BP and the BeSt InTro (paper 1 and 3) the primary analyses were intention-to-treat (ITT) analyses based on the randomization groups (RGs). That is, trial participants were analysed in the group to which they were randomized regardless of which treatment they actually received or the extent of treatment they received (393). Secondary analyses were per protocol analyses based on which antipsychotic in the randomization sequence that ultimately was initiated at study inclusion. Baseline comparisons in all papers were conducted with SPSS software (version 17.0, 23.0 and 24.0) (394) by means of exact χ^2 tests for categorical data and one-way ANOVAs for continuous data. For baseline comparisons between those lost to follow-up before retesting and those who were retested, independent samples T-tests were used for continuous data and exact χ^2 tests for categorical data.

3.6.1 BP

Paper 1

Change of depressive symptoms was analysed in R (395) by means of linear mixed effects (LME) models (396). Since the aim in paper 1 was to investigate the overall change during the follow-up period, the LME model was considered to be the analysis of choice for this purpose. The model uses all available data and handles different numbers of visits, as well as different intervals between visits and has demonstrated superior statistical power when the missing data is non-ignorable (397). For multiple comparisons, Benjamini–Hochberg adjustments were applied. Power estimations

were conducted in R by means of LME models. The initial CDSS sum score and within-person variation were based on the results of a previous model (381). Baseline CDSS sum was assumed to be around 6. Differences in CDSS sum score reductions between trial drugs of 20% (corresponding to 1.2 points difference in CDSS-sum over 2 years) were considered clinically relevant and a 10% reduction (0.6 points reduction in CDSS over 2 years) was entered for the supposed least effective drug. Thus, slopes corresponding to 10%, 30%, 50% and 70% reduction in CDSS in the respective drug groups were entered into the model. The initial CDSS sum score was set at 5.7 points in the model and an estimated drop-out rate of 3% per month was used. For each level of power 10,000 simulations were run. Based on these premises for the power calculations, the trial should have 80% power to detect statistically significant differences among the drugs with 45 subjects in each treatment group and 90% power with 55 subjects in each group.

Paper 2

Trajectory analyses are applicable for the assessment of symptoms and sub-dimensions and were conducted with the CDSS sum score as outcome. First, we established a latent growth curve model (LGCM), as LGCM is a flexible method which applies well to analyses of repeated measures as a function of time, includes estimation methods that handle missing data and models the individual levels and changes in addition to the mean level and change over time (398). Secondly, predictors were added to the model (grouping of diagnoses: schizophrenia spectrum vs. diagnoses of non-spectrum psychoses, antipsychotic naivety, gender and the PANSS positive sum-score). Then, a growth mixture model (GMM) (399) was conducted to identify unobserved sub-populations with different depressive symptom-trajectories. To select the best fitting GMM model and hence the number of trajectories, different model fit indices, likelihood-ratios and relative class frequencies were considered (398, 400). Finally, differences in clinical characteristics between trajectory-groups were investigated. Latent Growth Curve (LGC) and Growth

Mixture Models (GMM) were analysed in Mplus 7.4 (400). The LGCM- and GMM-methods are further elaborated in paper 2.

3.6.2 BeSt InTro (paper 3)

Latent Growth Curve modelling (LGCM) in Mplus version 8.3 (401) with the CDSS sum score as outcome was chosen as the statistical method for the primary analyses due to the strengths of the model in a clinical dataset as the present one. The applicability and strengths of the model are outlined in the paper 2 statistical paragraph and in more detail in the separate publications and manuscripts. Power estimations were conducted in R (395) by means of linear mixed effects (LME) models, equivalent to the strength analysis as described in paper 1, however with some slightly differing inputs entered into the model as the drop-out rate was predefined as 5% per month and the CDSS sum score reductions of 10%, 35% and 70% defined as clinically significant differences in change in the randomized groups. Simulations showed that the BeSt InTro would have >90% power to detect significant differences among the drugs with 48 subjects in each of the three treatment groups. Statistical methods are described in more detail in the manuscript of paper 3.

3.6.3 Post-hoc analyses

The original power-analysis showed, based on selected thresholds of clinical relevant differences in the antidepressive effectiveness between the drugs, that the trials were sufficiently powered to find statistically significant differences. For the purpose of the dissertation, post-hoc analyses in R (395) (paper 1) and in Mplus (401) (paper 3) were conducted. A non-linear model was tested for the data in paper 1 to investigate if this model fit more closely to data. The results will be presented. Moreover, in order to shed light on the probability that the negative results could be explained by insufficient power for depression as a secondary outcome, as elaborated in the secondary outcome-paragraph of the introduction (265-267), post-hoc analyses of statistical strength were conducted, based on the actual data in the BP and the BeSt

InTro (effectiveness-estimates of the study drugs, number of participants, dropout etc.). The number of participants, keeping the effectiveness estimates of the trials unaltered, in which power would exceed 80%, was determined with simulations in R and Mplus (395, 401) changing only the participant number. In the same way, simulations were run only changing the effectiveness differences between the drugs in order to find the effectiveness differences where "power" would exceed 80%. Such post-hoc "power" analyses are heavily debated in the literature and will be discussed in paragraph 5.2.6, page 106.

3.7 Approvals and ethical considerations

The BP and the BeSt InTro were conducted in accordance to the World Medical Association Declaration of Helsinki (409). Both trials were approved by the Regional Committee for Medical Research Ethics West-Norway and for BP also the Norwegian Social Science Data Services. Funding of both projects were from the Research Council of Norway and Haukeland University Hospital - Division of Psychiatry, in addition to funding from the Western Norway Regional Health Authority and participating hospitals in the BeSt InTro. Neither the BP nor the BeSt InTro received any financial or other support from the pharmaceutical industry.

BP

The Regional Committee for Medical Research Ethics allowed eligible patients to be included before informed consent was provided, thus entailing a clinically relevant representation in the study. The approval was granted to a two phase design: The first was the quality assurance phase from admission to discharge or 6 weeks at the latest which was approved without the requirement of informed consent as this phase included only elements of best clinical practice. The objective of this phase was to assure that psychotic patients were offered best-quality guideline-concordant assessments and treatment for psychosis, using the first-line antipsychotic drugs available at the time of the study (risperidone, olanzapine, quetiapine and ziprasidone). The second phase (research phase) was based on informed consent

provided at discharge or after 6 weeks at the latest. This included invitation to visits and tests at 3, 6, 12, and 24 months after admission. In this part of the project there were procedures beyond usual clinical standard, such as collections of data for use in psychiatric basic research within genetics and brain functioning. The study enrolment started in March 2004 and was completed in February 2009.

BeSt InTro

In addition to the approvals mentioned above, the BeSt InTro was approved in Norway by the Norwegian Medicines Agency. In Austria the trial was approved by the Etikkommission der Medizinische Universität Innsbruck and the Austrian Federal Office for Safety in Health Care (BASG). Clinical monitoring according to ICH-GCP (International Conference on Harmonisation - Good Clinical Practice) (410) was in Norway conducted by the Department of Research and Development, Haukeland University Hospital and in Austria by the Clinical Trial Centre at the Medical University Innsbruck. Participants had to be able to provide and to sign informed consent before the RCT inclusion and randomization. The BeSt InTro was conducted in accordance with Good Clinical Practice (GCP) standards (410) and with the Norwegian Health Research Act (411). The first patient was included 20th of October 2011 and the final visit of the last participant was the 21st of December 2017.

4. Results

4.1 Paper I

Thirty-three percent of participants in the BP were female, 44.2% antipsychotic-naïve, mean age was 34 years and 54.9% had a diagnosis within the schizophrenia spectrum disorders. Demographics and clinical characteristics, updated for the purpose of the thesis, are presented in Table 3. The mean doses in milligrams per day were 14.5 for olanzapine, 339.3 for quetiapine, 3.3 for risperidone and 100.3 for ziprasidone-treated groups. The mean serum levels in nanomoles per liter were 100.4 for olanzapine, 398.2 for quetiapine, 81.4 for risperidone and 122.9 for ziprasidone. In the BP the main findings were significant time-effects showing a steady decline in depressive symptoms in all medication groups. Pair-wise comparisons (ITT) demonstrated no statistically significant differences between the medication groups in the reduction of the CDSS sum score. Neither did sensitivity analyses restricted to the first 90 days, the exclusion of affective psychoses and substance-induced psychoses, nor did separate analyses in the groups with CDSS sum score >6 or ≤ 6 show statistically significant differences. A power-analysis indicated power between 80% and 90% with the number of participants randomized in order to reveal clinically relevant differences. A flowchart updated for the dissertation is presented in Figure 1, p. 60. A total of 96 of the 226 participants (42.7%) had a CDSS sum score >6 points at inclusion. Thirty participants (26.5%) changed their first-chosen SGA during follow-up. Eighty (74.1%), 28 (25.9%) and 7 (6.5%) patients received additional benzodiazepines, antidepressants and mood stabilizers, respectively. There were no differences among the study drug groups in the use of these additional psychotropics. Anticholinergics were prescribed for 6 (23.1%) in risperidone-treated participants 3.4% for olanzapine, 0 for quetiapine and 18.5% for ziprasidone (exact χ^2 test: p=0.009).

Table 3: Demographic and clinical characteristics in the BP at baseline.

Characteristics	Randomization Groups								All Patients (N=226)	
	Risperidone (N=57)		Olanzapine (N=54)		Quetiapine (N=52)		Ziprasidone (N=63)			
	N	% (CI)	N	% (CI)	N	% (CI)	N	% (CI)	N	% (CI)
Gender										
Male	41	71.9 (60.2-83.6)	34	63.0 (50.1-75.9)	35	67.3 (54.5-80.0)	42	66.7 (55.1-78.3)	152	67.3 (60.7-73.3)
Ethnicity										
White	50	87.7 (79.1-96.2)	49	90.7 (82.9-98.4)	49	94.2 (87.9-101)	57	90.5 (83.3-97.7)	205	90.7 (86.9-94.5)
Antipsychotic naive	21	37.5 (24.9-50.0)	20	37.0 (24.1-49.9)	28	53.8 (40.2-67.4)	30	48.4 (36.1-60.7)	99	44.2 (37.7-50.7)
Alcohol last 6 mths										
None	16	28.1 (16.4-39.8)	10	18.5 (8.1-28.9)	9	17.3 (7.0-27.6)	12	19.4 (9.6-29.2)	47	20.8 (15.5-26.1)
Misuse	3	5.3 (0-11.1)	5	9.3 (1.6-17)	10	19.2 (8.5-29.9)	5	8.1 (1.4-14.8)	23	10.2 (6.3-14.1)
Drugs last 6 mths										
None	32	61.5 (48.9-74.1)	38	73.1 (61.3-84.9)	36	72.0 (59.8-84.2)	38	66.7 (55.1-78.3)	144	68.2 (62.1-74.3)
Misuse	11	21.2 (10.6-31.8)	9	17.3 (7.2-27.4)	7	14.0 (4.6-23.4)	11	19.3 (9.6-29)	38	18.0 (13.0-23.0)
Diagnosis[1]										
Schz and rel.	27	50.9 (37.9-63.9)	20	38.4 (25.4-51.4)	23	44.2 (30.7-57.7)	26	44.1 (31.8-56.4)	96	44.4 (37.9-50.9)
Acute	7	13.2 (4.4-22)	15	28.8 (16.7-40.9)	12	23.1 (11.6-34.6)	12	20.3 (10.4-30.2)	46	21.3 (16-26.6)
Drug-induced	10	18.9 (8.7-29.1)	6	11.5 (3-20)	7	13.5 (4.2-22.8)	6	10.2 (2.7-17.7)	29	13.4 (9-17.8)
Affective	4	7.5 (0.7-14.3)	6	11.5 (3-20)	7	13.5 (4.2-22.8)	6	10.2 (2.7-17.7)	23	10.6 (6.6-14.6)
Rest	5	9.4 (1.8-17)	5	9.6 (1.7-17.5)	3	5.8 (0-12.2)	9	15.3 (6.4-24.2)	22	10.2 (6.3-14.1)
	Mean	**SD/CI**	**Mean**	**SD/CI**	**Mean**	**SD/CI**	**Mean**	**SD/CI**	**Mean**	**SD/CI**
PANSS Total	74.3	12.9/70.1-77.7	75.1	14.0/71.3-78.9	74.8	14.3/70.8-78.8	72.2	12.7/69-75.4	74.0	13.4/72.2-75.8
PANSS Positive	18.8	4.5/ 17.6-20.1	20.8	4.5/ 19.6-22	20.2	4.0/19.1-21.3	19.6	4.5/18.5-20.8	19.8	4.4/19.3-20.4
PANSS Negative	21.5	7.5/19.5-23.4	18.5	7.7/16.4-20.6	19.9	7.1/17.9-21.9	18.9	7.1/17.1-20.7	19.7	7.4/18.7-20.7
PANSS General	34.0	6.2/32.3-35.6	35.8	7.4/33.7-37.8	34.8	7.4/32.7-36.8	33.7	6.3/32.1-35.3	34.5	6.8/33.6-35.4
CDSS	6.7	5.7/5.2-8.2	6.5	4.7/5.2-7.8	6.4	4.6/5.1-7.7	6.4	6.0/4.9-8.0	6.5	5.3/5.8-7.2
GAF-F	31.0	5.3/29.6-32.4	30.6	5.3/29.1-32	30.1	6.7/28.2-32	30.9	6.6/29.1-32.5	30.7	6.0/29.9-31.4
CGI	5.2	0.6/5.1-5.4	5.2	0.7/5.1-5.4	5.2	0.6/5.1-5.4	5.0	0.6/4.9-5.2	5.2	0.6/5.1-5.3
Age	33.8	13.0 (SD) range 18-67	31.8	12.1 (SD) range 18-72	36.9	13.7 (SD) range 18-72	33.9	14.6 (SD) range 17-73	34.1	13.5 (SD) range 17-73

Notes: N = number of patients; SD = standard deviation; Antipsychotic naïve = No life-time exposure to antipsychotic drugs before index admission; First admission = Index admission is the first admission to a mental hospital; Misuse = Misuse or Dependence according to Mueser et al; Schz and rel. = Schizophrenia and related disorders: Schizophrenia, schizo-affective disorder, acute polymorphic psychotic disorder with symptoms of schizophrenia, acute schizophrenia-like psychotic disorder, delusional disorder; Acute = Acute psychosis other than those categorized under Schz and rel.; Affective = Affective psychosis; Rest = Miscellaneous psychotic disorders. All diagnoses are according to ICD-10; PANSS = the Positive and Negative Syndrome Scale; CDSS = the Calgary Depression Scale for Schizophrenia; GAF-F =

the Global Assessment of Functioning, split version, Functions scale; CGI = the Clinical Global Impression, severity of illness scale; Cognition t-scores = Mean t-scores on the RBANS (Repeatable Battery for the Assessment of Neuropsychological Status). SD = Standard Deviation. CI = 95% Confidence Interval. [1] Patients with missing diagnoses are not included in list.

4.2 Paper II

The patient group studied in this publication was the same as in paper 1 (N=226). The main findings in the BP regarding predictors of the CDSS scores: A reduction in positive psychotic symptoms was associated with a reduction in depressive symptoms. The schizophrenia-spectrum subgroup had less depressive symptoms at inclusion. Gender and antipsychotic-naivety was not associated with the course of depression. The results regarding depressive symptom trajectories: A three-class model was chosen based on model fit data. The three class model showed one class (15.7%) starting at a very high level and then quickly decreasing to a low-level, one class had persistent high-level depressive symptoms (14.7%) and the largest class had persistent low-level symptoms (69.6%). While both the low level and the early response groups improved considerably regarding positive and negative symptoms, the high depression level group was generally treatment refractive. The antidepressant prescription rate was high in the persistently depressed group (65-88% in the 4 weeks to 6 months interval), in-between in the early response group (20-38% in the 4 weeks to 6 months interval) and lowest in the low depressive symptom level group (17-19%) (Table 4). X^2 and ANOVA-analyses showed that participants in the low depressive symptom group were significantly more often diagnosed within the schizophrenia-spectrum, displayed more disorganized symptoms and were less cooperative, characterized by lower levels of insight, a lower general psychopathology score, less hopelessness, negative symptoms and suicidal ideation. Alcohol misuse or dependence at inclusion was more frequent in the persistently depressed group than in both the low depression and the early response group. Symptoms of agitation (PANSS Excitement component) were lower in the persistently depressed group than in the two other groups. In the Latent growth curve model there was a significant reduction in CDSS sum score the first part of the follow-up (baseline to discharge or 6 weeks) with a mean duration of 4.1 weeks. The following small reduction until 6 months was

not statistically significant. The statistical model showed close fit with the data and the results after excluding primary affective psychoses were almost identical. In these analyses 3 participants were excluded in the high depression level-group, 11 in the early response group and 11 in the low level group, overall 11% (N=25) of the 226 participants.

Table 4: Antidepressant prescription rate within trajectories

	4 weeks		3 months		6 months	
	Schiz n/N (%)	non-schiz n/N (%)	schiz n/N (%)	non-schiz n/N (%)	schiz n/N (%)	non-schiz n/N (%)
High level group	6/9 (67)	5/10 (50)	3/3 (100)	4/5 (80)	2/3 (67)	3/4 (75)
Early response group	0/5 (0)	4/13 (31)	0/2 (0)	3/6 (50)	0/2 (0)	1/3 (33)
Low-level group	10/48 (21)	2/24 (8)	5/20 (25)	1/16 (6)	2/17 (12)	3/10 (30)

n = number within diagnostic subgroup using antidepressant
N = number within diagnostic subgroup at visit

4.3 Paper III

Of the 144 participants 35% were female, the mean age was 31.7 years and 39% were antipsychotic-naive. Forty-seven percent of participants had a Calgary depression sum score >6 at inclusion. Tables of baseline-characteristics, depressed vs. not-depressed cohort, model-results, flow-chart and figures are included in paper 3 of the thesis. The mean study drug doses used were for amisulpride 396.9 mg, aripiprazole 14.6 mg and olanzapine 12.3 mg and study drug serum-levels are reported in Supplementary table 5 in paper 3. There were no statistically significant differences between the study drugs regarding depressive symptom reduction, although amisulpride had the steepest reduction. No statistically significant differences between the medications in reduction of CDSS were found in per protocol-analyses, neither. A linear-model power-analysis showed that the trial had 92% power to detect statistically significant differences among the drugs with 48 subjects in each of the three treatment groups based on predefined clinically relevant differences between the drugs. CDSS item

score-reduction followed the same pattern for all items. Sensitivity analyses restricted to the time of de facto administration of the study drugs showed substantially unaltered results. Separating the participants in a non-depressed or less depressed group (CDSS≤6) and a depressed group (>6) showed no differences in effect between study drugs in the depressed group. There were no statistically significant differences between the study drugs in the prescription of antidepressants within the sub-cohorts.

4.4 Post hoc-analyses

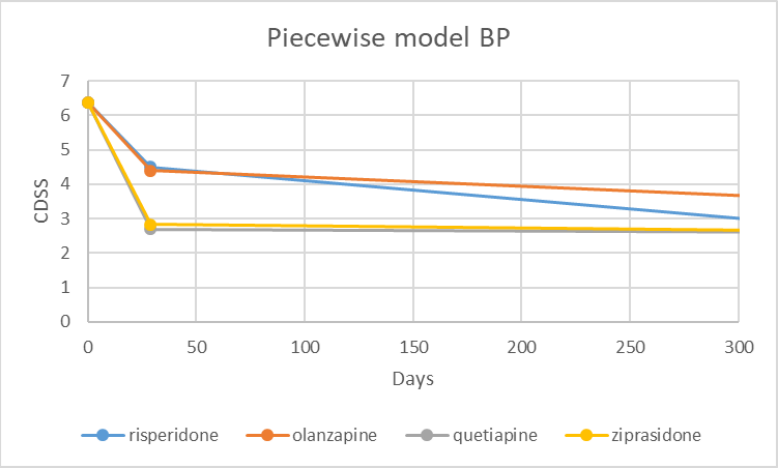
4.4.1 BP

Non-linear model of paper 1-data

Two non-linear models were tested for the paper 1-data in R (395). A model similar to the paper 3-model specified with slopes for each assessment interval proved difficult to apply for the investigation of post-hoc "power", probably due to the substantial drop-out rate with few remaining participants at 12 and 24 months and as the time-variable, due to a substantial variability in the attending-time of visit 2, had to be re-specified such that the alternative models were not directly comparable. Thus, a piecewise model was tested. This model is similar to the model in paper 2, with one change factor from baseline to visit 2 (≈ 4.1 weeks) and a second slope from ≈ 4.1 weeks to 24 months. This model retained a random intercept for each patient as in the original model. Comparing this model to the original linear model of paper 1 showed a better fit with regards to AIC (Akaike Information Criterion) with a reduction from 2825 to 2817, but a poorer fit with regards to BIC (Bayesian Information Criterion) with an increase from 2854 to 2863. BIC is stricter than AIC with regards to the number of parameters in the model, but the AIC-reduction shows that the piecewise model fitted closer to the data. The piecewise model is presented in Figure 2. Ziprasidone and quetiapine had the steepest reduction the first 4.1 weeks and then levelled out. Risperidone had the steepest reduction from 4.1 weeks to 24 months.

However, like in the original linear analysis, no statistically significant differences between the drugs were found, neither in the 1st nor the second interval (detailed results not presented). Baseline CDSS score in this model was 6.4 and at 12 months olanzapine had a model-based CDSS reduction of 2.8 (45% reduction) while quetiapine, ziprasidone and risperidone all had a reduction of 3.7 (58% reduction).

Figure 2 Post-hoc piece-wise model BP



Post-hoc power-analyses

Results of post hoc-"power" analyses based on the piecewise model described above is reported for the entire study period (2 years), due to the substantial drop-out and small effectiveness differences which made 12 month "power"-estimates difficult to attain. Conducting simulations with the piecewise model showed that in about 50% of simulations a statistically significant finding emerged in either slope 1 or 2 between the medications, thus post-hoc "power" was 50%. As described under methods 3.6.3 increasing the number of participants in model-simulations, keeping the effectiveness estimates of the trials, until a level in which power would exceed 80% was calculated, requiring about twice the trial size (450 patients). Effectiveness differences had to be increased with 50% in order for power to exceed 80%.

4.4.2 BeSt InTro

Strength of findings were reanalyzed in Mplus (401) within the non-linear model of paper 3, an LGCM Simulation Model with Random intercept Fixed slope. In this model baseline CDSS was 6.7, aripiprazole had a reduction of 2.4 in CDSS (36%), olanzapine a reduction of 2.6 (39 %) and amisulpride 4.0 reduction (60%). Power had to either be calculated per each assessment-interval (7 intervals in the BeSt InTro), overall linearly (12 month linear model as in the original power-analysis) or per specific time intervals within the non-linear model. Thus, we chose to only present findings for the baseline to 12 month interval within the non-linear model for simplicity reasons and in order to more clearly compare findings to other naturalistic studies where 12 months is the main follow-up period. Post-hoc "power" with the actual data was 36% for aripiprazole and 30% for olanzapine. Effectiveness differences had to be increased with 50% for aripiprazole and with 60% for olanzapine in order for power to exceed 80% with regards to finding statistically significant differences to amisulpride at 12 months. Finally, study size in simulations had to be increased to 500 to reach 80% power to find statistically significant differences from amisulpride for the aripiprazole change at 12 months and >600 for olanzapine.

5. Discussion

5.1 Discussion

The discussion will be structured as follows: First, a separate discussion of paper 1 and 3 as both addressed the antidepressive effectiveness of antipsychotics. Further, the results from paper 2 concerning course of depression after a psychotic episode will be discussed, then clinical implications will be examined before ending with a discussion of the methodology of the trials. Strengths and limitations are accounted for in the separate discussions (5.1.1-5.1.3) and in the "Methodological considerations" sub-sections (5.2.1-5.2.6).

5.1.1 Anti-depressive effectiveness

Summary

In paper 1 (412) and 3 the main findings were a time-dependent reduction in depressive symptoms in all medication groups (olanzapine, quetiapine, risperidone and ziprasidone in paper 1 and amisulpride, aripiprazole and olanzapine in paper 3) and no significant differences in improvement between the medication groups. Secondary analyses in the BP indicated that these findings were robust and sustained even after affective psychoses and substance-related psychoses were excluded. For the BeSt InTro sensitivity analyses focusing on diagnostic subgroups were not conducted as the participants as defined by the inclusion criteria were limited to the schizophrenia spectrum. The BeSt InTro investigated two SGAs which were not studied in paper 1 (amisulpride and aripiprazole). Olanzapine was the only SGA studied in both trials.

Comparisons to naturalistic, pragmatic and observational trials

In line with other pragmatic, randomized trials like the EUFEST, CAFE and CATIE studies significant differences in the anti-depressive effectiveness between the SGAs were not found (262, 263, 318). In the results-section 3.6.3-paragraph regarding post-hoc-analyses, a percentage reduction over 12 months was calculated. In the BP olanzapine had a CDSS reduction of 2.8 (45% reduction) while quetiapine, ziprasidone and risperidone all had a reduction of 3.7 (58% reduction). In the BeSt InTro figures were aripiprazole: 36% reduction, olanzapine 39% reduction and amisulpride 60%. The percentage figures for the CDSS-reduction in BP and BeSt InTro were comparable to figures from similar effectiveness-trials, however slightly lower than first-episode-studies: For comparison, depressive symptom-reduction was 30-40% in the medication groups in CATIE (263), 65-79% in the EUFEST-groups (262) and in the CUtLASS-trial 36.4% in the FGA-group and 27.5% of the SGA-group (258), amounting to less than the suggested clinically meaningful drug-difference of 1.3 change in the CDSS (251), except for the comparison of amisulpride and olanzapine in the EUFEST (262), which was in favour of olanzapine (difference 1.5 in the reduction of CDSS), although not statistically significant.

The CATIE study (263), however, did conclude with a small antidepressive superiority for participants randomized to quetiapine in those with a CDSS score >5.

The EUFEST (262), CAFE (318) and CATIE studies differ from the BP (Table 3 of the thesis) and BeSt InTro (Table 1 in paper 3) studies in participant inclusion characteristics. The CATIE study investigated patients with chronic schizophrenia with a mean age of 40 years, ¾ male, 60% white participants, a baseline CGI of 4, 30% depressed (≥6 CDSS) and PANSS total 76. The EUFEST and CAFE studies were first-episode studies with a mean age of 25 and antipsychotic-naivety in 33% or 24%, respectively. In CAFE ¼ were female, 50% of white ethnicity, PANSS total was 74 and CDSS 13 and 70% discontinued study drug while within EUFEST-participants 40% were female, 94% white, 31% dropouts, PANSS total 88 and 9% depressed. The BP and BeSt InTro trials included participants both with first-episode and more chronic illness, however with a preponderance of younger patients. The CUtLASS

trial (258) randomized patients to either SGAs or FGAs, not to individual drugs, and found no group-differences in the antidepressive effectiveness of FGAs vs. SGAs (mean age 40, ¼ female, PANSS total 72, CDSS 6.8 and dropout 17%). Of non-randomized observational naturalistic trials a large German observational study (319) found no group-differences in the antidepressive effectiveness of FGAs vs. SGAs, however did not report between-drug differences. Of these study participants ½ were female, age was 41 years, 14% FEP and CGI 5.3. The large Eli Lilly-sponsored SOHO-study (321-323), with mean age 35, 46% female, 16% antipsychotic naïve, CGI 4.3, CGI depression 3.3, found that olanzapine was superior to quetiapine and risperidone in depressive symptom reduction and at the 1-year follow-up also superior to amisulpride. However, firm conclusions were hampered by the observational design. Moreover, comparisons between the SOHO study and the BP and BeSt InTro are impeded by, among other, the substantially different study populations, which in the BP were acutely admitted and in she SOHO were recruited from outpatient treatment. An Israeli naturalistic trial (N=131) found no differences in antidepressive effectiveness between clozapine, olanzapine and risperidone (320), mean age was 37, 42% female. PANSS total 99, HAM-D 15.5. A small Italian naturalistic observational study (324) was not powered to investigate between-drug differences for atypical antipsychotics for depressive symptoms .

We could not replicate the finding of a superior anti-depressive effect neither of quetiapine in patients with elevated CDSS scores in the CATIE trial (263), nor the superiority of olanzapine in the SOHO-study (321). In fact olanzapine had the smallest reduction in the BP and close to the smallest reduction in the BeSt InTro, although not statistically significant. This may be due to a statistical type II-error as the BP and BeSt InTro studies were not primarily designed to investigate antidepressive effectiveness. This aspect of the BP and BeSt InTro-results will be elaborated in the post-hoc analyses paragraph 5.2.6 focusing on power.

In addition there was no trend in the BP for a superior antidepressive effect of quetiapine. To some surprise in the BP risperidone had the greatest reduction in depressive symptoms and olanzapine had the smallest reduction, with a trend towards

statistical significance between the drugs (p=0.0583). Based on theory and earlier trials this is surprising as risperidone as accounted for in the introduction has among the highest D2-occupancies among the SGAs which has been linked to dysphoria (127, 128). Indeed, risperidone has proven inferior to olanzapine and quetiapine in efficacy trials for depressive symptoms in schizophrenia (76, 301) and was not superior vs. neither placebo nor FGAs for depression in schizophrenia in two meta-analyses by Leucht et al (382, 413). However, the power of the review was restricted as the meta-analysis of risperidone vs. placebo included only two studies of risperidone (414) and Study Ris-USA-72.

In sub-analyses in the purpose of this thesis of the group with CDSS sum score >6 in the BP at baseline, quetiapine actually had the greatest reduction with a model-based reduction in CDSS sum score over one year of 4.67 while the olanzapine-group actually had a minor increase in the CDSS sum score corresponding to 0.24 CDSS points over one year, a change from the model-based baseline value of 10.5 in the CDSS. This difference was however not statistically significant (p=0.22), which again could be attributed to a power-problem in the sub-analyses. The subgroup with CDSS sum score >6 included affective psychoses. This trend may indicate a superior antidepressive effectiveness of quetiapine in the most depressed psychotic patients, which is in line with the CATIE-findings (263), although this possibility remains hypothetical.

In essence, the BP and BeSt InTro supplements the limited evidence from randomized, pragmatic and from observational, naturalistic antipsychotic trials that there are no substantial overall differences in the anti-depressive effectiveness of the studied SGAs in psychotic patients. The possibility remains however, that effectiveness differences may exist for the depressed subgroups in effectiveness-trials, but remain unrevealed as depressive symptoms are not sufficiently pronounced in these trials that also have investigated depressive symptoms as a secondary outcome (265).

Comparisons to efficacy-trials

Thus finalizing the effectiveness comparisons, several efficacy trials are relevant for the discussion of the BP and BeSt InTro findings: Dollfus et al, in a double-blind 8-week trial of olanzapine vs. risperidone for post-psychotic depression, had insufficient power to reach firm conclusions due to problems with the inclusion of participants.. Both drugs were effective, with no statistically significant differences between the drugs (415) in line with the effectiveness results of the data in this thesis (the BP). The 76 participants' in the Dollfus' trial mean age was 29, 30% were female and baseline MADRS score was 27. Olanzapine and ziprasidone were found effective for comorbid depression in schizophrenia in a double-blind 24-weeks efficacy trial of 394 patients by Kinon et al (416). In this trial there were no statistically significant differences in mixed-effects model analyses of the antidepressive efficacy of the medications neither at 8 weeks nor 24 weeks. The study group were outpatients, 37% completed the study, PANSS baseline total was 79 and MADRS 27. The non-significant difference between olanzapine and ziprasidone in the BP replicates these efficacy findings for the first time in a pragmatic trial. Ziprasidone has also formerly in a trial with 256 patients by Zimbroff et al been found to be equally effective to aripiprazole for depressive symptoms in schizophrenia (309). Sixty-nine per cent completed that trial, 1/3 were female, 1/3 of white ethnicity, mean age was 40, PANSS baseline total 98, but the depression severity or change as measured by CDSS was not presented. As aripiprazole and ziprasidone were not investigated in the same trial in the manuscripts of this thesis, we could not compare their effectiveness head-to-head. Aripiprazole vs. olanzapine have not been compared in trials reporting depression as an outcome in schizophrenia, thus the BeSt InTro findings of equal effectiveness are novel. Amisulpride and olanzapine have formerly been investigated in two double-blind multi-centre efficacy trials of 8 weeks (N=85) and 6 months (N=377) where both medications were found to be effective against co-morbid depression in schizophrenia (303, 304). There were, however, no statistically significant differences in the antidepressive efficacy between amisulpride and olanzapine in the trials, in line with the findings in the BeSt InTro. The study

population of this double-blind efficacy trial was more narrowly defined than in the BeSt InTro and included participants with significant depression at inclusion. The results of the BeSt InTro replicate the efficacy-findings of non-significant antidepressive differences in a randomized pragmatic effectiveness setting for the first time.

Findings in view of pharmacodynamic properties

All study drugs in the BP, in theory, have antidepressive properties either due to 5-HT_{2A}-antagonism (32, 34, 146) (all trial drugs), 5-HT_{1A}-agonism (ziprasidone and to a lesser extent risperidone and quetiapine) (34), antagonism of adrenergic α_2-(olanzapine and risperidone) or α_1-receptors (all trial drugs) (34) or due to inhibition of trans-membrane monoamine transporters (147-150) (quetiapine and ziprasidone). Potential differential antidepressive effectiveness between the drugs due to pharmacologic differences were not revealed and the described dysphoric response to risperidone in former trials, theoretically linked to D_2-blockade (128, 302), did not seem to affect the antidepressive effectiveness of risperidone in the BP, which actually had among the largest CDSS-reductions in the BP. In theory, the other favourable pharmacologic properties of risperidone regarding antidepressive effect, could counteract D_2-blockade.

Supportive for the findings of a significant depressive symptom reduction, but no significant differences between amisulpride, aripiprazole and olanzapine in the BeSt InTro, is that all three medications were among the SGAs superior to FGAs for depressive symptoms in a Leucht meta-analysis (382) and amisulpride and olanzapine were superior to placebo in another meta-analysis (413). Additionally, in theory all the 3 SGAs have antidepressive pharmacodynamic properties as accounted for in the introduction paragraph 1.4.2 (32, 34, 146), despite their pharmacodynamic profiles differing substantially (Table 2). These pharmacodynamic properties included antagonism of serotonergic 5-HT_{2A}-receptors (aripiprazole and olanzapine), agonism of 5-HT_1-receptors (aripiprazole, partial agonist) (34), antagonism of adrenergic α_1/α_2-receptors (34) and limbic selectivity (amisulpride) (32). Thus, the favourable

limbic selectivity on the dopamine system by amisulpride (32) may balance out the antidepressive effects of olanzapine and aripiprazole potentially mediated by their superior affinity for the serotonergic receptors and increased norepinephrine release due to actions at the α_1- and α_2-receptors (146). The head-to-head comparison of amisulpride and aripiprazole in paper 3 is the first reported in literature. Amisulpride has formerly been shown to have a superior anti-depressive efficacy compared to haloperidol and risperidone, however noting that haloperidol- and risperidone-doses were high in that trial, which theoretically may have led to more D_2-blockade and thus more dysphoria (302). As we did not directly compare amisulpride and risperidone in the same trial, we have not analysed them head-to-head.

Clinical significance

In the introduction paragraph 1.4.5 about the CDSS-scale, the lacking definition of clinically significant changes or clinically significant effect differences between treatments for depression in psychotic disorders was reviewed, as measured by the CDSS. A difference of 1.3 points has been suggested as a minimum clinically important differences in a conference poster (251). This poster is the only lead from the literature to assist a consideration of clinical effectiveness. We investigated the overall change of the CDSS-measure and did not consider response as could be defined by a >50% CDSS-reduction or remission that could be defined by a score below a specified CDSS-level. In the BP piecewise model the difference in CDSS-reduction between olanzapine and the 2 other drugs was 0.9 points or 45% vs. 58% reduction. We do not consider this difference clinically significant and the percentage difference was smaller (13%) than the assumed clinically relevant of 20% in the power-analyses. Limiting our assessment of clinical significance is the practically total lack of consensus within this field of research. In the BeSt InTro the greatest difference in CDSS-reduction at 12 months was 1.6 points between amisulpride and aripirazole or 24% difference which both were above suggested clinically significant cut-offs. Thus, this effectiveness difference might be considered clinically significant. As this difference was not statistically significant though, this will be discussed further in the 5.2.6 post-hoc-analyses paragraph.

Antidepressant prescription rates

The frequency of antidepressant prescription was surprisingly low in the BeSt InTro (3.6-31.3%) even in the sub-cohort depressed at inclusion (10-25%), and markedly lower than in the BP where, at different assessments, 22-88% of depressed participants were administered antidepressants (Table 4). The rate in the BP was highest in the trajectory consisting of the persistently depressed group. Overall in the BP between 25.7% and 30.8% of the total group of participants that attended the 4 weeks-6 months visits received antidepressants which is in line with the antidepressant prescription rate at baseline in the CATIE-study (417) and slightly lower than in a US veteran cohort (418), which both however included markedly older and more chronically ill patients. As both the BP and the BeSt InTro were conducted within the same hospital and departments, there seems to have occurred a change of threshold for when to initiate antidepressant treatment during or following a psychotic episode in the time passed between the trials. We do not have any leads as to why this markedly changed over a decade within the same institution. The unclear antidepressant treatment recommendations may be one possible cause. The findings could however even be chance findings not representing a systematic shift of initiation of antidepressant treatment, as we only have data from the 2 RCTs over the years and do not have prospective medication records for all psychotic patients at the hospital over these years.

5.1.2 Courses/trajectories of depression

Summary

There is a risk of underestimating the impact of enduring depressive symptoms after an acute psychotic episode as a great proportion of acutely psychotic patients have depressive symptoms that respond to antipsychotic treatment of the episode. Our findings in paper 2 indicate however, that only half of patients with depressive symptoms at admission respond adequately to standard, naturalistically registered, treatment of the psychotic episode. The main findings for depression-course in acute-phase psychosis in the BP were that there was best support for a 3-class model with

one persistently depressed group, one depressed, but rapidly improving group and one large group (2/3) with few depressive symptoms both during and after the psychotic episode.

Rapidly improving group

The rapidly improving group and the finding that positive psychotic symptoms predicted depressive symptom reduction in paper 2 supports the observation in several earlier trials that the clinical improvement in the depressive dimension significantly correlates with the severity of the positive psychotic symptoms and their improvement (61, 85, 91, 93, 99-102, 117, 419). Regarding the proportion of improving depressed patients, our finding that half of the depressed patients remitted rapidly is in line with an early, however small, key trial (420) and with a FEP-study with a one year follow-up of 92 patients (369). Hypothetically, the rapidly improving group could consist of patients which were spontaneous remitters if for instance drug-induced psychoses and psychotic depression were overrepresented. However, we found no differences between the persistently depressed group and the rapidly improving group in this regard except for more non-schizophrenia spectrum diagnoses in the rapidly improving group and more alcohol-abuse in the persistently depressed group. The diagnosis spectrum difference was no longer significant after the exclusion of psychotic depression-diagnoses, while the rapidly improving trajectory group was still identified. The only other significant differences were found in comparison with the less depressed subgroup, thus the possibility that the rapidly improving group could be due to frequent spontaneous remitters in this particular group, seems unlikely.

Treatment refractory group

The persistently depressed participants remained depressed despite a high rate of antidepressant prescription. In schizophrenia depressive symptoms resistant to treatment are in fact quite rarely reported in the literature despite the fact that the low responsiveness of post-psychotic depressive symptoms to treatment received attention as early as in 1967 (115). Corresponding to the results of paper 2 (421), a similarly

substantial - however vastly ranging - proportion of patients with treatment refractory depressive symptoms has been found in some earlier studies; Cotton et al (195) in 14.2% and Fond et al (422) in 44.1% of initially depressed patients and Möller and von Zerssen (85, 423) showed in a small study (N=72) that about ¼ followed a persistently depressed course throughout the study. The same researchers found in another trial that in 56% of 237 patients a relatively long-lasting depression during the clinical stay was observed and 17% remained depressed at discharge (85, 140). Upthegrove et al (369) in a study of 92 FEP-patients found that 30% of the participants experienced depression in the acute phase throughout the follow-up at 6 and 12 months and Leff et al (100) showed in a small trial that when psychotic symptoms failed to respond to neuroleptic drugs, depressive syndromes remained unchanged. Strian et al (99) observed that among initially depressed patients, less than half had persistent depressive symptoms, but the authors did not report characteristics of persistently depressed patients.

Characteristics of persistently depressed patients

Concerning characteristics, in some studies depressed schizophrenia patients have been shown to be characterized by more global, positive and negative symptoms overall than non-depressed patients, including significantly more residual symptoms at discharge or follow-up at 6 months (71, 95, 424). The finding of more pronounced residual symptoms in these studies is in line with our findings for the persistently depressed group. Concerning remission however, Riedel et al (71) found that significantly less depressed patients reached remission criteria, mainly due to residual negative symptoms and unusual thought content. A South-African study found that depressive symptoms were similar in remitters and non-remitters (425). Schennach-Wolff et al (187) observed that persistently depressed patients were characterized by multiple episodes of psychosis. Alcohol misuse or dependence at inclusion in the BP was more frequent in the persistently depressed group than in the two other trajectories while agitation was less pronounced in the persistently depressed group than in the two other groups. While alcohol use disorders are well known to be

closely linked to major depression (426), this relation is less studied in primary psychotic disorders (72, 79, 190, 191). Our findings replicate for the first time the recently published results of Fond et al (422) of more alcohol abuse specifically in persistently depressed psychotic patients. However, as the Fond cohort were outpatients this is to our knowledge the first time this has been shown in acute phase psychosis. Concerning treatment resistant schizophrenia recent findings demonstrate that in this sub-group the presynaptic dopamine disturbance is absent (427). If there is such a common neurochemical background for treatment resistant depressive symptoms in schizophrenia and general treatment resistance in schizophrenia remains speculative. However, as refractory positive psychotic symptoms are closely associated with lack of improvement of depressive symptom, antipsychotic treatment resistance seems to be invariably linked to persistence of depressive symptoms as well.

Group with less depressive symptoms

The group with limited or no depressive symptoms was larger in our study compared to some earlier, smaller trials finding that about ¼-½ of patients with acute phase psychosis were not depressed (85, 95-97, 114). Due to a lacking consensus of how to define depression, the definition and identification of depression varied between the trials, thus possibly contributing to the varying results. The findings that participants in the BP low depressive symptoms-group were characterized by more disorganized symptoms, less cooperation, lower levels of insight, lower general psychopathology-score, less hopelessness, lower negative symptoms and less suicidal ideation, may indicate that they belonged to a group characterized by more chronic psychotic illness. However, the patients in the group were not statistically significantly older than the patients in the two depressed groups. In correspondence with our finding of a reduced insight in the group with low depressive symptoms, as accounted for in the introduction several former publications have showed that increased insight is associated with depression in schizophrenia (187, 192-195). The finding of more negative symptoms in depressed patients vs. non-depressed are also in line with former trials (187). Observing more disorganized, fragmented symptoms or more

symptoms of agitation/aggression being associated with less depressive symptoms has been reported in a former observational study, where the authors hypothesized that these patients were prevented from perceiving their difficult situation and thus were "protected" from depressive affect (131).

Post-psychotic depression

Concerning post-psychotic depression we found that depressive symptoms rarely appeared de novo in or after the psychotic episode, but was present during the early phase of the psychotic episode. This is in line with several earlier publications (140, 187, 369, 419, 428). The hypotheses why a de novo post-psychotic depressed group did not emerge may be several: One obvious option is that there was no emerging post-psychotic depressed group, but that these patients had depressive symptoms in the acute-phase, possibly overshadowing the depressive symptoms and leading to a clinical observation of a post-psychotic debuting depressive syndrome. A second option is that there was such a group, but that it was small and not detected within the power of the model or thirdly; that these patients were members of the large drop-out group. Several papers support the first hypothesis; that patients with schizophrenia do not show a depressive reaction in the recovery or post-psychotic period: A North-American follow-up study with a categorical approach to depressive symptoms found that depression was highly prevalent in the acute phase but did not find evidence for a post-psychotic debut of depression (98). The study was, however, small (N=27) and has been criticized for its definition of post-psychotic depression (110). Drake et al (186) found in 257 FEP patients that mood improved over time and argued that their findings casted doubt about the post-psychotic depression-construct. On the other hand several studies have found depression debuting in the post-psychotic period, Birchwood et al (114) in as many as 36% independent of an increase in psychotic symptoms, Mandel et al (74) in 25%, Knights & Hirsch in 15% (117), Bressan et al in 16.3%, Möller and von Zerssen (85, 139, 140) in 14-15% and Leff (100) in 3 out of 11 (27%). In the Birchwood studies around 2/3 of the defined PPDs were depressed at onset, thus lowering the estimate of de novo PPDs. One of the studies omitted the

time-criterion of 12 months as defined by the ICD-10 criteria (7, 106). Thus, in summary the results for de-novo depression in the post-psychotic period are conflicting. In some of the earlier trials the conclusions are blurred by the context of FGA-treatment and less valid depression rating instruments, which may have led to detection of depression that was related to EPS or negative symptoms. Our results strengthen the observation that depressive symptoms observed shortly after admission for a psychotic episode or during early antipsychotic treatment rarely emerges de novo and should be seen frequently as closely related to the psychotic episode and are in line with the early observations of McGlashan (104) from 1976: "Depression was commonly present for both groups during the acute phase of psychosis and remitted over time along with the rest of the psychotic pathology but the depressive picture remitted more slowly for patients who were post-psychotically depressed». If the number of de novo emerging depressions in the post-acute phase in the BP was small, it would not be supported in the best supported model, however, not even the 4-class or 5-class model identified a de novo PPD group (figures not shown in neither paper 2 nor the thesis). The possibility remains, however, that potential de novo PPDs dropped out of the study and were not identified due to attrition. In the study by Riedel et al (71) more depressed (55%) than non-depressed (37%) patients dropped out of the trial, although the difference did not reach statistical significance. Mandel et al (74) in a study from 1982 found that depressed patients were significantly less likely to complete the study (19% vs. 49%). Schennach-Wolff et al (429) found in a clinical trial of acutely ill FEP patients that 10% dropped out due to depression, suicidal tendencies or somatic disorders. However, in the BeSt InTro attrition analyses (analyses/results not included in papers 1-3) actually demonstrated that less depressed participants were less likely to attend the next study visit at two time-points. Thus, results are somewhat conflicting regarding depression as a predictor of attrition in trials of antipsychotic treatment.

Antipsychotic-naivety as predictor of depressive symptom reduction

As meta-analyses have shown that FEP patients respond better in overall PANSS/BPRS score-reduction than chronically ill patients with schizophrenia and that drug naivety was a determinant of response (313, 430), it may be suspected that this would apply to depressive symptoms in the acute phase as well, however this is not well known. Antipsychotic-naivety is likely to be more strongly associated with first-episode psychosis than with multiple episodes and a more chronic course and serve as a proxy for FEP. It has been shown that treatment response is more favourable in FEP patients (431). We could not find evidence of a superior effectiveness in antipsychotic-naïve patients for depressive symptoms.

Re-examination of trajectory sub-classification

We found that the rapidly responding depressive group was of about the same size as the non-responding depressive group. However, with statistical models, there is rarely a perfect fit. A re-examination shows that some patients have been classified in the low-depressive group while having depressive symptoms at inclusion, and may be considered to belong to the rapidly responding group which then would be greater than the non-responding group. Thus the low depression group was smaller than the one emerging in the supported model, which is more in line with findings in former trials.

5.1.3 Clinical implications

Despite several of the findings being in line with established knowledge, this evidence is primarily retrieved from FGA-trials (92, 99, 117, 131, 134, 139) which is not necessarily valid in the current treatment-context in high-income countries where SGA-treatment dominates. Moreover, older trials have a more pronounced risk of bias due to among other less specific depression assessments. Thus, the need for methodologically more robust and clinical relevant data is obvious. Furthermore, only a scarcity of this knowledge has made its way to treatment guidelines (239, 273, 276,

277, 279) and the dissemination of this knowledge is thus important in order to reach clinicians, patients and their caregivers and next of kins.

The results of paper 1 (412) and 3 do not provide evidence for any preferred choice of a specific SGA for the most depressed acutely psychotic patients. Rather, the results of paper 2 (421) underline the importance of unravelling depressive symptoms early, re-evaluating depressive symptoms repeatedly after initiating treatment of the antipsychotic episode and instituting the best available depressive symptom-focused treatment and care for the patients with depressive symptoms that do not respond to current treatment-as-usual of the psychotic episode. However, the evidence for specific interventions for depressed patients with schizophrenia remains limited although there are indications of a moderate effect of antidepressants and some promising results for CBT (128, 268, 269, 336, 337, 340). Despite the limited evidence for specific psychological interventions for depression in schizophrenia (336, 337, 340), demoralization and persistent depression may very well be amenable to a stable therapeutic relationship, continuity in treatment, prevention of despair and hopelessness and counteracting passivity and isolation, although the studies included in this thesis do not provide answers in that regard.

Consistent with a growing evidence base of SGA-treated psychotic patients, if SGAs induce dysphoric symptoms in psychotic primary psychotic patients, this seems to be a sporadic phenomenon (62, 67, 125, 128, 313) and the iatrogenic SGA-induced depressive episodes do not constitute a discrete subgroup in the treatment of acute psychosis. Based on BP and BeSt InTro data we cannot conclude that patients receiving SGAs with in theory less antidepressive pharmacodynamic properties - for instance risperidone with more pronounced D_2-blockade (127, 128) – are inferior concerning the antidepressive effectiveness.

The persistently depressed group identified in paper 2 (421) represents an on-going challenge in the treatment of schizophrenia. Depressive symptoms are not part of the Remission in Schizophrenia Working Group (RSWG) remission criteria of schizophrenia which limit the definition to core diagnostic symptoms of schizophrenia (432). In major depression the goal of treatment is remission as defined

by for instance HAMD criteria of the ACNP Task Force in Major Depressive Disorder (249) and the original remission criteria by Frank et al (250). In schizophrenia the bulk of the treatment efficacy focus has revolved around positive and negative psychotic symptoms, while the persistently frequently reported depressive symptoms and their known strong correlation with functioning and quality of life have received much less attention. This decision not to incorporate important symptoms contributing to functional impairment in the schizophrenia remission criteria has been criticized (433). Based on our knowledge of the debilitating, possibly neurotoxic consequences of ongoing non-remitting depression in primary affective disorders (434, 435), it is reasonable to suspect that non-remitting depression in primary psychotic disorders could have similar implications. Overall remission in First episode psychosis, defined by the current criteria, has been found to predict better quality of life and life satisfaction (429, 436). Thus, response- and remission-criteria for depression in schizophrenia should be defined and remission of depression in schizophrenia should be a target of treatment. The importance of adhering to the established guidelines for treatment-resistant schizophrenia (239, 273, 278) seems to be highly relevant for the persistently depressed group which is also persistently psychotic. The best documented and recommended intervention for treatment-resistance in adherent patients is to initiate clozapine treatment (437). It is vital that clozapine treatment is not unnecessarily postponed when there are treatment failures of at least two different antipsychotics. As a parallel, based on the knowledge and current findings of more substantially improving depressive symptoms in responding psychotic individuals, antipsychotics like amisulpride, olanzapine and risperidone which in some meta-analyses display a superior antipsychotic efficacy (35, 438-440) may reduce the amount of patients with post-psychotic refractory depressive symptoms.

5.2 Methodological considerations

5.2.1 The patient sample

Representativity

There was a substantial diagnostic overlap in the patient samples in the BP and BeSt InTro consisting of patients within the schizophrenia spectrum. However, there were also distinct differences as the BP-cohort was diagnostically more heterogeneous and had a wider diagnostic range. The patient samples due to the acute psychiatric ward recruitment setting are in our view highly relevant for daily clinical practice. Contrary to most clinical trials and in line with the pragmatic design, we did not define an upper age limit of 65 years. As the evidence-base regarding antipsychotic treatment of elderly psychotic patients is limited it is important that patients in this age group are offered participation in drug trials. Despite deciding upon not defining an upper age limit for participation, very few participants were >65 years (in the BeSt InTro only 2 participants). Moreover, not excluding participants with comorbidity in the form of drug or alcohol problems or suicide risk, adds to the evidence of drug treatment effectiveness that is valid for real-world patients as these comorbidities are highly frequent in psychotic disorders. The resulting heterogeneity was sought handled with sensitivity analyses which added to the robustness and applicability of the results.

The psychiatric health-care system in Norway is available to all inhabitants, is publicly funded and organized within catchment areas. The privately financed health-care system providing psychiatric care in Norway comprises a very small part of the treatment-facilities and is almost negligible when considered in the setting of the treatment of an acute psychotic episode. As the standard, all patients in need of acute treatment are referred to their local psychiatric centre or hospital. This organization indicates that the patient sample within the current catchment area is representative of the total population and hence that selection bias due to how health care is organized is unlikely. However, there may be differences between urban and rural psychiatry.

The catchment area of the BP and BeSt InTro is primarily urban, thus the implications may primarily be valid for city-dwelling populations.

As the participants (at visit 2 in the BP and at inclusion in the BeSt InTro) had to provide a valid informed consent and to cooperate at assessments, the most severely ill patients were probably not included in the study. This represents a selection bias which however cannot be avoided in consent-based studies. Except for health registry studies few studies are able to provide evidence for this most gravely ill subgroup of psychotic patients. Nonetheless, the group that could be included is still highly symptomatic with relevance also for some of the most severely ill patients, however not for patients eligible for antipsychotic injection-treatment and clozapine treatment or for patients with organic disorder or a manic psychosis. Moreover, selection bias were reduced by the few exclusion criteria and wide inclusion criteria.

Regarding representativity for clinical populations, 30.5% of those assessed for eligibility in the BP and 40.1% of the BeSt InTro assessments were included. For the remainder of this paragraph the inclusion/eligibility-fraction specific for the BP will be discussed: Enrolment started March 2003 until 2008, week 26, but full details on enrolment were only registered from 2006, week 31 until 2008, week 26. The main reason for not being included was lack of cooperation. All psychotic patients admitted were considered for eligibility which probably contributed to the rather low inclusion rate. As the screening-log of the BP was not registered in detail in the first phase of the trial, the percentage of eligible participants that were included (30.5%) stems from week 31 in 2006 to study end. Thus, we do not know if the eligible vs. randomized portion would have been the same if these data were collected from the study beginning. Considerations of the trial representativity thus is affected by this uncertainty. However, we have no indications that the pattern of eligible participants or inclusions changed substantially from 2003 to 2008. There were no major organizational changes in this time interval that affected path of admission.

Characteristics

The gender-distribution was identical in the BP and BeSt InTro (1/3 female) and in line with former antipsychotic trials within schizophrenia (152, 257, 258, 318) while the mean age was in-between FEP-trials and trials with more chronically ill participants. The vast ethnic majority were white, in line with the cited European trials, while there were substantially less black participants than in the North-American trials. The ethnic representativity of the trials in this thesis is of course substantially different from Asian, African and South-American studies. The frequency of alcohol and drug abuse in the BP and BeSt InTro was slightly lower, but comparable to the CATIE, CUtLASS and EUFEST effectiveness-trials (where alcohol abuse ranged from 20% to 40% and drug abuse from 15% to 32%) (152, 257, 258) while most efficacy trials do not permit recruitment of participants with comorbid drug or alcohol disorders (64, 179). Antipsychotic naivety was actually more frequent than in the cited trials that reported naivety which were mainly FEP-studies with reported frequencies of naivety from 24% to 33% (152, 318). Thus, concerning demography the studies of the thesis are more comparable to FEP-studies from high-income countries than to trials of participants with more long-standing illness.

Challenges with depressive symptoms as a secondary outcome

As the BP and BeSt InTro were designed to be trials of antipsychotic effectiveness, the antidepressant effectiveness is a secondary outcome. Thus, the trials were not primarily designed to investigate effectiveness for depressive symptoms. As a consequence the statistical power was reduced as the studies were not ‘enriched’ for depression. If the trials were designed with depressive symptoms in primary psychotic disorders as the primary outcome, depressive symptoms above a defined threshold, for instance CDSS sum score >6, could have been selected as an inclusion criterion. In addition, as improvement of depressive symptoms during treatment of ongoing psychosis is subject to the influence of improvement in - among other - positive symptoms, restricting inclusion to patients with enduring depressive symptoms after

completed adequate antipsychotic treatment of the current psychotic episode may have resulted in a more "pure" estimate of the impact of the change in medication on depressive symptoms. In common with the BP and BeSt InTro, most of the naturalistic or pragmatic studies investigated depressive symptoms as a secondary outcome and hence did not systematically include depressed patients with schizophrenia (128). Thus, the moderate sized and small trials carry a substantial risk of being underpowered for the depression outcome.

Among the mentioned potential limitations of papers investigating secondary outcomes presented in the introduction paragraph 1.5.2 (265-267) some apply to the BP and BeSt InTro: sample biases e.g. possibly contributing to less pronounced expressions of secondary outcomes and less statistical power to detect effects on secondary outcomes and that aspects of the data collection may affect the generalizability to clinical populations. Most mentioned limitations do however not apply, thus consisting a strength: the available secondary outcome measure (the CDSS) was the desired one, the antidepressive reduction-hypotheses were pre-specified and inherent to the study designs and thus not guided more by availability of data than research hypotheses and the CDSS outcome was not more prone to missing data than the primary outcome of the BP and BeSt InTro (PANSS).

5.2.2 Design of the trials

Strengths

A major strength of both the drug trials is the randomized design. Another major strength is that power analyses were conducted and concluded that clinically relevant effects could have been disclosed with the current study size. Moreover, the funding of the studies being industry-independent adds to the strength of the trials, particularly to independence in the choice of design and in the conclusions. In summary, few of the methodological limitations outlined by Castle & Bosanac in trials for antidepressant efficacy apply to the papers included in this thesis (264). The few exclusion criteria, particularly that patients with severe depression or suicidality or

substance misuse could participate, secure a wider, more clinically relevant representation in the trials and reduces risk of selection bias. The BP was designed to mimic everyday clinical circumstances as closely as possible in order to increase representativity of the data. Serum levels were measured for almost all patients that were still medicated attending the visits in the BP and for 1/2-2/3 in the BeSt InTro and showed for the vast majority of patients that the serum levels were within accepted reference range for the drugs (data not shown in the papers or the thesis apart for mean serum levels and SD), however with a tendency towards lower levels in the beginning and the end of the BeSt InTro. Overall, medication adherence for the patients attending visits was good.

Limitations

Drop-out

Several aspects of the design contributed to challenges in interpreting data. Among other the long follow-up (2 years) contributed to the very low trial completion rate of 6.6% of the included participants. Drop-out may bias results for instance if the most ill patients systematically were lost to follow-up or if patients who experienced less antipsychotic effectiveness dropped out and this was unevenly represented between the trial drugs. These aspects are also discussed in the 5.2.6 “Missing at random”-paragraph. It has been shown that antipsychotic trial length predicts drop-out (383). Based on a Mixed Effects Regression equation for the drop-out rate in antipsychotic trials developed by Rabinowitz et al (383) the BP at 52 weeks would be predicted to have a drop-out rate of 43.8% compared with the actual rate of 85.4% while the BeSt InTro at study end (52 weeks) had a predicted drop-out rate of 48.2% compared with the actual rate of 58.3%. The substantial discrepancy between the predicted and actual drop-out rate in the BP may to some degree be explained by the permission to include and randomize patients before consent was provided and the required consent at the second assessment. This possible explanation may also apply to the greater drop-out rate than the CATIE-study where 63.6% of participants dropped out (383). The planned follow-up could have been shortened although the major drop-out (85% of

the total drop-out) in the BP occurred within 3 months. The problem with the large attrition rate of the BP and to a lesser degree, in the BeSt InTro, applies in a greater or smaller degree to all trials aiming at including psychotic participants (255, 380). Moreover, we attempted to lower drop-out with the flexible dosing-design, as flexible dosing has been shown to reduce attrition (385) and by reminding participants before the next follow-up. Not including a placebo-arm in the trial-design could reduce dropout as placebo-controlled trials have greater dropout rates (384). Another potential improvement to the methods would have been drop-out-analyses including contacting and interviewing participants who dropped out in order to more solidly conclude with the reason for drop-out and reason for drop-out. However, we did not have permission to establish contact with participants who did not respond to reminders of assessments or who had withdrawn consent. Moreover, in the BP there were generally no substantial differences in baseline clinical or demographic characteristics between those who were lost to follow-up before retesting and those who were retested, with the exception of a slightly greater PANSS negative sub-score for those lost to follow-up (20.8 vs. 18.5 points (independent samples T-Test: p=0.02; mean difference 2.3 points; 95% confidence interval (CI) 0.4-4.2)). Some of the challenges with dropout remain resistant to even the most robust study designs, as they are a result of the aspects of the psychotic disorders, like the lacking and unstable insight into the need for treatment, thus with remaining uncertainty in trial interpretations. Nevertheless, this aspect underlines the distinct methodological difficulties in providing needed long-term data of a sufficiently large proportion of psychotic patients to reach relevant, valid conclusions for patients.

Limitations with inclusion-criteria

The clinical inclusion criteria represented by a threshold of ≥ 4 in essential positive symptom-items of the PANSS, is practically applicable, in line with former antipsychotic trial-designs (318, 380) and was applied in the BeSt InTro as well. However, the varying definitions and lacking consensus of the definition of an ongoing psychotic episode, acute exacerbation or relapse in international research complicates comparisons (255).

The diagnostic inclusion criteria of the BP are rarely seen in other trials and thus add challenges in the comparisons with other studies (76, 262, 263, 318). In support of the rare inclusion design are the before-mentioned known challenges of diagnostic validity and the lacking stability of diagnoses in the long term (17-20). The diagnostically heterogeneous representation in the BP is realistic in a clinical setting, not the least as the trial had a substantial portion of first-episode participants with undetermined diagnoses (17-20). Retrospectively though, the decision to include bipolar and unipolar affective illness was a novel approach to trial design, resulting in small primary affective subgroups of which it was difficult to make robust conclusions. On the other hand, diagnosing first-episode patients continues to be a demanding challenge (17, 19, 20), and the delineation between a primary depressive episode with psychotic features and a primary psychotic episode with depressive features remains blurry where information from a longer-term course is needed to reach a more certain diagnostic conclusion. In addition, the heterogeneity was, to as large an extent as possible, handled with sensitivity sub-analyses, conducting reanalyses excluding participants with drug-induced psychoses and psychotic depression. Sensitivity analyses in paper 1 and 3 also included analyses restricted to the first 3 months of the trials and restricted to the period of actual use of study drug. The decision to include participants with drug-induced psychoses is in line with the knowledge that a large proportion of these patients with a severe delay are diagnosed with primary psychotic disorders (18). However, the inclusion criteria were specified as when the condition did not resolve within “a few days”. This could preferably by specified as at least 48 hours, in line with diagnostic criteria for substance-induced psychoses F1x.5 in the ICD-10 (7) to distinguish this state from acute intoxication from a psychoactive substance.

As a CDSS-score above a predefined threshold was not an inclusion criterion, a substantial part of participants had a low CDSS sum score at baseline. This characteristic may have constituted a risk of a floor-effect, e.g. that the outcome-variable score is too small as a starting point for a potential significant outcome-reduction. However, 43% in the BP and 47% in the BeSt InTro had a CDSS-score >6.

The authors of the CDSS in a paper investigating antidepressive reduction in the CATIE-trial, applied >5 as a threshold for depression (263), which would result in the depression cohort being 50% in the BP and 51% in the BeSt InTro. Moreover, the power analysis of both trials indicated sufficient power with the assumed CDSS-mean baseline score which in the BP power-analysis was based on former pragmatic trials like the EUFEST (262) and the BeSt InTro baseline was based on BP data (412). The actual baseline CDSS score in the LME linear model of the BP was equal to the one applied in the power-model (5.7), In the BeSt InTro the assumed baseline CDSS was lower in the trial model (5.4) than in the power-model (5.67), thus the risk of a floor-effect was slightly more probable in the BeSt InTro.

Limitations with the randomization

Randomizing to a sequence of the study drugs was chosen to aid the naturalistic design as participants could have former negative experiences with the first study drug on the list, and in discussion with their doctors thus choosing the next drug in the sequence. Attempting to establish a design reflecting everyday practice, more stringent design features were abandoned, including double blind treatment conditions. This decision may have introduced bias, both from the patients' and the raters' perspective. The blinding of raters should reduce bias, but the blinding may unintentionally have been broken in particular circumstances. In clinical trials where primary analyses are ITT, a fraction of patients always end up not taking the assigned randomized drug or a different drug. This circumstance was facilitated in the BP and BeSt InTro with the randomization to a sequence-approach, but this approach may have been too facilitating, thus resulting in more frequent rejection of the first randomized drug, in the next instance leading to less transparent results, in the form of larger differences between the ITT- and PP-analyses. If clinicians or patients had preferences for particular drugs, bias may have been introduced. For instance, in the BeSt InTro, among the participants randomized to aripiprazole and olanzapine who chose another study drug, the vast majority chose amisulpride (14/18 = 78%). Hypothetically, amisulpride may have been the preferred drug at the study sites.

However, a more probable cause is that amisulpride in the years 2012-2017 among the study drugs in Norway by a large margin was the least prescribed, aripiprazole in-between and olanzapine by far the most frequent (441). These patients had probably tried more SGAs than participants not changing the drugs, indicating more treatment failures, possibly contributing to a smaller probability of symptom-improvement. Similar aspects apply to the BP as well, as ziprasidone in the West-Norway region in 2004-2009 was by far the least prescribed of the study drugs (441), while olanzapine was about twice as frequently prescribed as quetiapine and risperidone. However, the number of participants choosing a different drug was not statistically different between the randomization groups.

Other limitations with design

The assessment time-points in the BP were few at the start of the trial, but more regular on follow-up. In particular visit 2 represents a problem – as the time-point for the visit was defined as 6 weeks from baseline or at discharge if discharged before 6 weeks. Thus, the time of assessment of the participants at this visit ranged from 0.7 to 11.1 weeks (mean 4.1). Retrospectively, this visit should have been defined more narrowly in order to reduce bias. The range in the other visits of the trial was also too wide. Lessons learnt from the design-challenges of the BP led to a more strict design for the assessment-schedule in BeSt InTro with tests scheduled for narrowly defined time-points with stringent deviation margins. The assessment intervals were in addition more frequent in the early phase after baseline where most of the symptom change takes place (1 week, 3 weeks and 6 weeks).

5.2.3 Assessments

Calgary Depression Scale for Schizophrenia

The choice of the CDSS (164, 240) as the primary outcome assessment-tool is a strength due to its widely documented specificity and validity for depression in schizophrenia and its sensitivity for change (232, 234-238, 240). However, a

limitation regarding the conducted assessments of the trials is that although reliability testing was conducted for the PANSS-ratings in the BP and BeSt InTro with satisfactory results, the remaining assessment scales and psychometric instruments were not subject to reliability training and testing. As this lacking reliability information also applies to the main outcome in the three present papers - the CDSS - this represents an apparent limitation, contributing to some uncertainty in interpretations. However, the CDSS is designed with simple, instructive descriptions for the sub-scoring of single items and as a semi-structured goal-directed interview, thus very likely contributing to more reliable scoring (240). In addition, the CDSS has demonstrated good inter-rater reliability (240, 442). As reviewed in the introduction paragraph 1.4.5, a too large correlation between items in a scale may indicate item redundancy, particularly if inter-item correlations (Cronbach's α) are above 0.9 (245, 246). Papers investigating inter-item correlations do not indicate such large correlations, however (241-243, 442) and Addington et al have shown that none of the CDSS items did not contribute significantly in discriminant analysis, which does not indicate that redundancy is a problem (442). A limitation of the scale is that it is designed for use by an experienced rater (240). In the BP and BeSt InTro assessments were conducted by experienced raters who were clinicians.

Diagnostic process and other assessments

Not systematically conducting diagnostic interviews in the BP is an apparent limitation as clinical diagnoses are likely to be less reliable. This limitation was reduced in the BeSt InTro by basing diagnostic conclusions on conducted structured clinical interviews, performed by psychiatrists or specialists in psychology in the study group. Although inter-rater reliability scoring was determined and satisfactory for the PANSS-ratings in the BP and satisfactory PANSS inter-rater reliability deemed necessary for approval of raters in the BeSt InTro, repeated reliability testing was not conducted, which represents a limitation as we cannot be sure that the initial reliability for the PANSS continued throughout the trials. The reporting of retrospectively collected information for instance concerning alcohol and drug abuse,

may be subject to recollection bias (443), thus contributing to uncertainty in the interpretation of these variables. A thorough chart review was conducted in order to reduce the impact of recollection bias and other data that were challenging to retrieve from the participants at study visits. As we did not record psychotherapeutic and psychosocial interventions conducted during the trials a quantification of the contributions of these different treatment-modalities thus cannot be determined.

5.2.4 Treatment

In accordance with the pragmatic design of the BP and BeSt InTro, no predefined requirements for the length of the medication cross-taper periods were set, but left to the clinicians to decide. Nor were wash-out periods of previously used antipsychotics required before randomization. This naturalistic non-restrictive design adds to challenges in interpreting data, as there may have been remaining effects of the formerly used antipsychotic that was attributed to the study drug (255). This may constitute a confounding source. However, the randomization should secure that this effect was evenly represented in the different randomization groups.

As we did not include a placebo-group or an FGA-arm in the trials, we are not able to determine if the studied SGAs are superior to placebo or specific FGAs nor determine the magnitude of the depressive symptom reduction specifically related to the SGA treatment vs. the effects attributed to the naturalistic co-prescription of psychotropics e.g. antidepressants and hypnotics and to other constituents of treatment-as-usual, including supportive therapy and CBT. In Norway, inclusion of a placebo group would however be deemed as unethical (444), as SGAs thoroughly have proven efficacy for psychosis and as acute psychotic episodes constitute such a debilitating illness. However, an FGA group could have been added, as in the CATIE (263) and the EUFEST studies (262), but the aim of the studies in this thesis were to investigate SGAs head-to-head and the trials were insufficiently powered to investigate additional medication groups.

A double-blind design could have been chosen (254). Such a double-blind design would have added to the methodological strength and to reduce risk of interpretation

bias. Moreover, there is an established consensus that a double-blind design is the gold standard for evidence concerning drug trials (254, 393). However, in selecting a double-blind design, the trials would then no longer be pragmatic trials as was intended. In addition, double-blind RCTs are even more resource demanding and costly than single blind trials and were not considered feasible for the BP and BeSt InTro. Few, if any, research-organizations outside the pharmaceutic industry have access to such resources. The fact that investigators knew all patients were receiving an active treatment possibly could influence ratings in a positive direction.

Possible confounding of attributing differences in depression improvement between the study drugs related to hypothetical differences in the rate of prescriptions of antidepressants, anticholinergics and anxiolytics/hypnotics between the SGAs were investigated by t-tests which showed that only anticholinergics were significantly more frequent in any randomization group, namely the risperidone group. This is most likely due to more EPS in the risperidone-group. As anticholinergics in some trials (445) have been shown to be associated with antidepressant effects, we cannot rule out that anticholinergics may have led to less depressive symptoms in the risperidone group. The small differences in the BeSt InTro in co-prescription of mood stabilizers at baseline and anticholinergics at 3 months also represent a potential confounding factor. However, we consider this possible confounding as small and not substantial.

5.2.5 Ethical considerations

The choice and approval in the BP to include participants before informed consent was provided contributed to the perhaps most important limitation in paper 1 and 2: the substantial attrition rate. In medical research the provision of informed consent from the participants is fundamental (446). However, the assessment of the ability to give informed consent can be highly complex in clinical trials recruiting patients with psychotic disorders (447). The first phase of the BP was defined as the hospital's quality project and informed consent was thus not required by the ethics committee. If the BP should be reconducted and redesigned, from a methodological point of view it

would not be the preferred design as there would probably have been fewer drop-outs if consent was compulsory at inclusion. On the other hand, trials necessitating informed consent, although consent being an undisputable vital defining ethical criterion, systematically will exclude a substantial proportion of the most gravely ill psychotic participants , thus leaving a gap in evidence for the treatment of these severely ill patients. Contributing to the dilemma, these patients will probably receive the medication when it is approved for marketing, despite the lack of evidence in this patient sub-group. Trial inclusion of patients without informed consent is justifiable on 2 conditions: That no other context exists in which the research question can be answered, and that all patients get clear clinical benefit from whatever treatment they are allocated to (409). Some clinical trials investigating the treatment of severe, acute psychiatric states, have been conducted with an exception from the compulsory informed consent in order to maintain representativity (448, 449). In the BP all patients got clear clinical benefit of the treatments they were allocated to. At the time of the design of the trial however, it may be argued that other trials contexts that involved informed consent could have answered the research questions. Such a design would however have led to fewer included participants belonging to the most severely ill subgroup, thus reducing representativity. Another challenging aspect of the design permitting inclusion of participants without compulsory informed consent is that at the point of visit 2, where consent was sought, participants may have felt obliged to sign consent as randomized treatment already was initiated. The high-quality health-service in Norway available for all patients should however counteract such a perceived obligation for participants. In the BP and BeSt InTro the design and included assessments were the results of a trade-off between required assessments and the resulting strain on the project participants.

5.2.6 Statistical considerations

Choice of method

Although the LME statistical models (396) apply well to antipsychotic drug trials, due to the inevitable missing data challenges, and as LME models make use of all the

data, there are limitations with the LME-models as well: One important disadvantage is that there are many possible variations of these statistics, making them relatively non-transparent and less intuitive (255). In line with a paper discussing different results from the PANSS changes in the EUFEST trial with different statistical methods (Last Observation Carried Forward (LOCF) vs. Mixed models (450), applying the traditional LOCF-method to handle missing data instead of the LME analyses could have disclosed different results in the BP and the BeSt InTro. However, it is important to predefine and retain the statistical method ahead of trial initiation. In addition, the LOCF-method, which is a very simple imputation technique using the last observation before the patient discontinues as an endpoint, has been criticized for either being too conservative in the estimate for the treatment outcomes or to liberal, depending on the setting. Moreover, the LOCF-method is based on obviously wrong assumptions, namely that the dropouts would not have changed if they had stayed in the study (255, 451).

Missing at random-assumption

However, mixed models, like the LME-model applied in paper 1 and latent models like the LGC applied in paper 2 and 3, pose challenges in that they assume that the missing data are missing at random (MAR) (398, 400, 452). In line with the EUFEST antipsychotic trial (453) and probably most clinical trials within psychiatry, we do not have information about the participants that dropped out of the study and thus are not able to definitely conclude that missing data are MAR. Nevertheless, methods like Maximum Likelihood (ML) (398) as applied in paper 2 and 3 outperform LOCF based analyses and the challenges of MAR also apply to LOCF (454). A third possibility would be to impute data with more advanced statistical methods than the LOCF, like Multiple Imputation (MI) (455). However we find a detailed discussion of these methods outside the scope of this thesis.

Choice of predictors in paper 2

Regarding choice of predictors of depressive symptom course in paper 2 we decided to omit negative symptoms despite including for instance positive psychotic

symptoms in the model. This decision was due to the specificity of the CDSS as a measure of depressive symptoms isolated from negative symptoms (234, 236). However, some trials have observed an overlap between depressive and negative symptoms as measured by the CDSS (168, 169, 422). In retrospect, a negative symptoms dimension could have been included as a predictor in paper 2, in order to determine potential associations despite the specificity of the CDSS. For the purpose of this this thesis we conducted Spearman correlations, due to the non-parametric distribution of the CDSS sum score, between PANSS negative sum score and CDSS sum scores at each visit, as a measure of the associations of the scales. The correlations for the BP were none to very weak with correlation coefficients (r) ranging from 0.01 to 0.262, only significant at visit 2. For the BeSt InTro correlations were small to weak with correlation coefficients from 0.040 to 0.355, significant at visit 3-6 and visit 8. These findings add further to the independence of the CDSS measure from negative symptoms. The same discussion applies to the decision to omit extrapyramidal symptoms from the model, which were available from the UKU side effects scale (392). However, in order to keep the ratio between the sample size and the number of predictors including interaction terms as high as possible, we decided not to add further predictors to the model, as this would have resulted in reduced estimation precision and statistical power (398). Despite this, the sum of extrapyramidal symptoms from the UKU could have been compared between the trajectory groups. The dosage of the SGAs is another omitted candidate for inclusion in the prediction-analysis. Confidence-intervals were not systematically reported in paper 1 and 2: This represents a limitation, as the reporting of 95% confidence intervals (456) makes it easier to interpret results, including the uncertainty of findings.

Post-hoc analyses and statistical power

There is a probability that there in fact were effectiveness-differences between the drugs in the BP and BeSt InTro, but that inferior statistical power led to non-significant differences. Although power-analysis indicated a statistical power >80%

for the depression outcome, how precise the indicators in the power-analysis fit with the actual trial data must be discussed. Moreover, post-hoc-analyses results must be discussed. The rationale behind the post-hoc-analyses is given in the 3.6.3 and results of these analyses in the 4.4.1 paragraphs. However, power-analysis are intrinsically conducted in the planning of a trial. Thus, conducting post-hoc analyses based on the data as they turned out in the trial are not in essence power-analyses anymore and such post-hoc analyses capitalizes on p-values or sample effect sizes resulting in estimates for post-hoc "power" which are difficult to interpret, as discussed in several method-papers (402-404). The topic is debated in literature with some researchers advocating the utility of such analyses (405, 406) and most warning against such use (407, 408). Non-significant p-values always correspond to low observed powers (402, 403).

BP

In the BP assumptions in the original power-analysis in paper 1 was a CDSS baseline score of 5.7, drop-out rate of 3% and 20% differences in CDSS-reduction between medication-groups (10-70%). For comparison CDSS baseline in original linear model was 5.67, thus in excellent correspondence with the baseline entered in the original power model, while regarding drop-out 33 participants attended the 12 month visit compared to 157 in the actual data, thus the drop-out rate assumption was vastly underestimated, contributing to substantially less power. Finally, effectiveness differences were smaller (13%) than those considered clinically relevant. Consequently, despite the very substantial drop-out rate which was much more pronounced than assumed in the power-analyses, effectiveness differences were outside the scope of presumed clinical relevance. The post-hoc-analyses in this thesis showed that within the study size effectiveness had to be increased with 50% or study size had to be doubled in order to find statistical differences in slope 1 or 2 of the piecewise model with a power >80%. To conclude, with the actual effectiveness differences and a resulting need to include 450 patients for the differences to be

statistically significant within standard power demands, this indicates that the actual differences are not clinically significant.

BeSt InTro

In the BeSt InTro assumptions in the power-analysis was a CDSS baseline score of 5.67, a drop-out rate of 5% per month and differences in CDSS-reduction between medication-groups (10, 35 and 70%). For comparison the actual CDSS baseline score in the linear model was 5.4, contributing to reduced power, while regarding drop-out 60 participants were not lost to follow-up at 12 months compared to 78 based on the drop-out rate assumption, which fit much closer to the actual drop-out than the BP power analysis, but still was slightly underestimated, thus contributing to reduced power. The assumption in the power-analyses of a 10% CDSS-reduction in the least effective drug-group, which applied both to the BP and BeSt InTro power-analyses, may have been a too small effectiveness-assumption as comparable effectiveness trials rarely showed less than 25-30% reduction for the least effective drugs (258, 263). Thus, power may have been smaller than estimated. Finally, effectiveness differences were slightly above (1.6 points between amisulpride and aripirazole) the only literature-based definition considered clinically relevant (251). Summarizing, underestimation of drop-out rate, a too low assumption for the least effective drug and assuming a greater baseline CDSS than the actual all contributed to reduced power. Actual effectiveness differences were just above presumed clinical relevance. The post-hoc-analyses in this thesis showed that within the actual study size, effectiveness had to be increased with 50-60% or study size had to be tripled in order to find statistical differences in a latent contrast model with a power >80%. Thus in conclusion, the actual effectiveness differences and a resulting need to include 500-600 patients for the differences to be statistically significant within accepted power demands, the actual differences were not deemed clinically significant.

6. Conclusion

1. There was a significant reduction of depressive symptoms over time with antipsychotic treatment of a psychotic episode for all the studied second generation antipsychotics

2. Significant differences in the effectiveness of SGAs for symptoms of depression in psychosis were not found. Statistical power was however smaller than estimated. Still, we can make no recommendations concerning choice of any particular SGA for targeting symptoms of depression in a patient acutely admitted with psychosis.

3. Three different courses of depression in acutely psychotic patients were identified

4. Of clinical importance, we identified an early response group and a treatment-resistant group

5. Half of the depressed patients remitted rapidly

6. For the persistently depressed group, antipsychotics and antidepressants (or other treatment-as-usual) do not work sufficiently

7. We did not find characteristics for those who had persistent depression

8. We could not identify post-psychotic depression that was not already there in the acute psychotic episode

9. Antipsychotic naïve patients had greater reduction of positive psychotic symptoms, but not of depressive symptoms.

10. Improvement of positive psychosis symptoms was associated with a greater reduction of depressive symptoms.

11. The schizophrenia spectrum participants had less depressive symptoms

7. Future perspectives

The Norwegian national guidelines for the treatment of psychotic disorders (239), and several other national guidelines (273, 276, 277, 279), are not updated with evidence supported by this trial, although some of the findings are replications of older trials that still have not been implicated in many guidelines. In future updates of guidelines it should be recommended to wait for the effect of antipsychotic treatment on depressive symptoms in an acute psychotic episode. In addition, the importance to focus on patients with depressive symptoms that do not respond adequately after initiated antipsychotic treatment, should be underlined. The crucial importance of this effort is obvious as the most devastating preventable consequence of enduring depression is suicide.

Despite that the papers of this thesis primarily provide evidence for the antidepressive effectiveness of antipsychotics, the literature-review unveiled that there is a distinct need to investigate and obtain evidence of more effective antidepressant treatment like for instance trials of depression-directed CBT (343) in primary psychotic disorders and SSRI and SNRI trials in enriched depressive cohorts of psychotic patients. Trials for the treatment of persistent depressive symptoms after a psychotic episode may be designed with different treatment arms. Trial arms may include antidepressants, CBT, switching to clozapine (437) and ECT (352) . Particularly the lack of CBT trials investigating depression efficacy in schizophrenia is surprising (340), as CBT efficacy is exhaustively documented in unipolar Major Depressive Disorder (335). Medications applied for novel indications as antidepressants - for instance ketamine - in case reports show promise also for depression in schizophrenia (457).

Although difficult to investigate in research, psychosocial interventions as a standard part of the treatment-as-usual (TAU) and thus also part of the naturalistic treatment in the BP and BeSt InTro, like for instance strengthening motivation, counteracting isolation and inactivity, promoting physical activity and training (44), fostering hope

(73, 123) and improving and optimizing the effect of the ward atmosphere and milieu therapy (52) are indisputably important parts of the comprehensive treatment of individuals with psychotic episodes. While it is challenging to design studies for isolated parts of the psychosocial interventions, comprehensive treatment-programs vs. TAU could be investigated with effect on depressive symptoms as outcome.

In the further work with data from the BeSt InTro for the outcome of depression we plan to investigate the relationships with the impact of voice hearing as measured by the revised Beliefs about Voices Questionnaire (BAVQ-R) (458). With the inflammation hypothesis of schizophrenia (459) receiving renewed attention after findings from genetic studies highlighting the complement system (460, 461), we plan to investigate associations between the vast array of inflammation markers from the BeSt InTro and depressive symptoms. Due to the substantial overlap in design between the BP and the BeSt InTro an opportunity would be to pool the trials in order to investigate depression outcomes with increased statistical power. Sub-cohorts in the trials like the participants with significant depressive symptoms or the persistently depressed, could be investigated in more depth, although the number of medication groups represent an enduring power challenge. We also aim to conduct path-analysis of direct antidepressive effects and indirect effects between depressive symptoms and EPS, negative symptoms, positive symptoms and to quantify these effects (179, 180). A qualitative research design was not considered feasible for the papers of this thesis, however may be a focus of future research. One possible qualitative design model would be to conduct in-depth interviews of remitted depressed individuals and persistently depressed patients to compare their experience of the impact of varying aspects of the illness and different parts of the treatment and care.

8. References

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9. Papers I-III

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RESEARCH ARTICLE Open Access

Anti-depressive effectiveness of olanzapine, quetiapine, risperidone and ziprasidone: a pragmatic, randomized trial

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Abstract

Background: Efficacy studies indicate anti-depressive effects of at least some second generation antipsychotics (SGAs). The Bergen Psychosis Project (BPP) is a 24-month, pragmatic, industry-independent, randomized, head-to-head comparison of olanzapine, quetiapine, risperidone and ziprasidone in patients acutely admitted with psychosis. The aim of the study is to investigate whether differential anti-depressive effectiveness exists among SGAs in a clinically relevant sample of patients acutely admitted with psychosis.

Methods: Adult patients acutely admitted to an emergency ward for psychosis were randomized to olanzapine, quetiapine, risperidone or ziprasidone and followed for up to 2 years. Participants were assessed repeatedly using the Positive and Negative Syndrome Scale - Depression factor (PANSS-D) and the Calgary Depression Scale for Schizophrenia (CDSS).

Results: A total of 226 patients were included. A significant time-effect showing a steady decline in depressive symptoms in all medication groups was demonstrated. There were no substantial differences among the SGAs in reducing the PANSS-D score or the CDSS sum score. Separate analyses of groups with CDSS sum scores > 6 or ≤6, respectively, reflecting degree of depressive morbidity, revealed essentially identical results to the primary analyses. There was a high correlation between the PANSS-D and the CDSS sum score ($r = 0.77$; $p < 0.01$).

Conclusions: There was no substantial difference in anti-depressive effectiveness among olanzapine, quetiapine, risperidone or ziprasidone in this clinically relevant sample of patients acutely admitted to hospital for symptoms of psychosis. Based on our findings we can make no recommendations concerning choice of any particular SGA for targeting symptoms of depression in a patient acutely admitted with psychosis.

Trial Registration: ClinicalTrials.gov ID; URL: http://www.clinicaltrials.gov/: NCT00932529

Background

Depressive symptoms are common in psychotic disorders, illustrated by point prevalence figures in patients with schizophrenia between 7-75% [1,2]. These figures vary due to different sub-populations and different definitions of depression. The modal rate has been estimated at 25% [2]. The identification of depression in this patient group is challenging for several reasons, including the overlap between depressive symptoms and the negative symptoms of psychosis and depressive features being common in the prodromal phase of schizophrenia [1]. Nevertheless, depression should be diagnosed and properly treated as it is associated with increased distress, poorer functional performance, a poorer quality of life, increased rates of relapse and increased mortality related to suicide [3-6].

Anti-depressive properties have been indicated for several second generation antipsychotics (SGAs) [7-11]. Different hypotheses exist regarding the mechanisms by which the SGAs mediate their anti-depressive effects, including antagonism of serotonergic $5HT_2$ receptors; agonism of $5HT_1$ receptors; antagonism of adrenergic α_2 receptors and inhibition of trans-membrane monoamine transporters [12-14]. The evidence for efficacy is strongest in bipolar depression in which some SGAs have

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become agents of first choice [10]. Pragmatic studies of anti-depressive effectiveness of SGAs in more heterogeneous, naturalistic samples with psychosis are scarce [15,16]. Short-term studies do, however, indicate anti-depressive effects of several SGAs in non-affective psychosis [17]. Olanzapine was superior to haloperidol in reducing depressive symptoms in a 6-week study [18]. In patients with treatment refractory schizophrenia, quetiapine was found to be superior to haloperidol in reducing depressive symptoms during the 8-week follow-up [19]. Both studies were sponsored by the pharmaceutical industry. Some studies have indicated a marked superiority of clozapine in reducing the risk of suicide and depressive symptoms compared to the other antipsychotics [20]. In some recent studies quetiapine has demonstrated anti-depressive properties in both clinically depressed and non-depressed populations [9,21,22]. There are indications that studies sponsored by the pharmaceutical industry selectively report data in favour of the sponsored drug [23].

Clearly, more long-term studies are needed on the highly prevalent occurrence of depressive symptoms in psychosis. In particular, comparative effectiveness trials of first-line SGAs funded independently of the pharmaceutical industry are called for in order to provide clinically relevant evidence on whether or not differential anti-depressive effectiveness exists among the drugs. We have previously reported the superior effectiveness of quetiapine on several outcomes other than depression [24]. The overall depression outcome was reported only briefly. Depression and depressive symptoms are, however, the main foci in the present study with a larger sample.

The primary aim of the present pragmatic, randomized study is to investigate whether differential anti-depressive effectiveness exists among olanzapine, quetiapine, risperidone and ziprasidone, in a clinically relevant sample of patients acutely admitted to a psychiatric hospital with psychosis. The hospital is responsible for all the acute admissions in the catchment area.

Methods

Study design

Methods have been described in more detail in a previous publication [24]. The Bergen Psychosis Project (BPP) is a 24-month, prospective, rater-blind, pragmatic, randomized, head-to-head comparison of the effectiveness of olanzapine, quetiapine, risperidone and ziprasidone. All patients were recruited from the Division of Psychiatry at Haukeland University Hospital with a catchment population of about 400,000. The BPP was approved by the Regional Committee for Medical Research Ethics and the Norwegian Social Science Data Services. Funding of the project was initiated by the Research Council of Norway, followed by the Western Norway Regional Health Authority and Haukeland University Hospital, Division of Psychiatry. The BPP did not receive any financial or other support from the pharmaceutical industry.

Patients

The Regional Committee for Medical Research Ethics allowed eligible patients to be included before informed consent was provided, thus entailing a clinically relevant representation in the study. Any investigation that was beyond normal clinical practice was introduced only after informed consent was obtained. Patients (age ≥ 18 years) were eligible for the study if they were admitted to the emergency ward for symptoms of psychosis as determined by a score of ≥ 4 on one or more of the following items in the Positive and Negative Syndrome Scale (PANSS): delusions, hallucinatory behavior, grandiosity, suspiciousness/persecution or unusual thought content [25] and were candidates for oral antipsychotic drug therapy. The inclusion was based on the presence of psychotic symptoms irrespective of diagnostic group, thus reflecting the diagnostic uncertainty commonly present in the early treatment phases in acutely admitted psychotic patients who are nevertheless in need of antipsychotic medication. Eligible patients met ICD-10 [26] diagnostic criteria for schizophrenia, schizoaffective disorder, acute and transient psychotic disorder, delusional disorder, drug-induced psychosis, bipolar disorder except manic psychosis and major depressive disorder with psychotic features. The diagnoses were determined by the hospital's psychiatrists or specialists in clinical psychology. Patients were excluded from the study if they: were unable to use oral antipsychotics because depot formulations were indicated, did not understand spoken Norwegian language, were candidates for electroconvulsive therapy as determined by the attending psychiatrists, were suffering from organic brain disorder - principally dementia or were medicated with clozapine on admittance. Patients suffering from manic psychosis or who, due to other behavioral or mental reasons, were unable to cooperate with the assessments were also excluded from the study. Patients with drug-induced psychoses were included only when the condition did not resolve within a few days and when antipsychotic drug therapy was indicated.

Treatments

The pragmatic design aspired to mimic the normal clinical situation with regards to treatment allocation without compromising the randomization which protects against systematic differences between groups that are not related to the treatment. Randomization to a sequence was considered the preferred method. At admission, a sealed and numbered envelope was opened by the attending psychiatrist and then the patient was offered

the first drug in a random sequence of olanzapine, quetiapine, risperidone or ziprasidone. The randomization was open to the treating psychiatrist or physician and to the patient. Both the treating clinician and/or the patient could discard the SGA listed as number 1 on the list because of medical contraindications to, or prior negative experiences with the drug. In that case the next drug on the list could be chosen. The same principle was followed throughout the sequence. A reason for discarding a drug was requested. In each sequence, the SGA listed as 1 defined the randomization group (RG). The actual SGA chosen, regardless of randomization group, defined the first-choice group (FCG). Further dosing, combination with other drugs or switching to another antipsychotic drug were then left at the clinician's discretion. Apart from sporadic use, the patients in the project could use only one antipsychotic drug, except during the cross-taper period associated with a change of antipsychotic drug. This is in correspondence with leading treatment guidelines which suggest combinations of antipsychotics be used only as a last resort [27]. In cases where concomitant use of more than one antipsychotic drug was inevitable, the patient could not participate in the project.

Assessments

Assessments were performed at the following points of time: at baseline, at 6 weeks from baseline or at discharge if discharged before 6 weeks from baseline and at 3, 6, 12 and 24 months from baseline.

The majority of assessments were performed by one trained investigator, EJ, assisted by HAJ and RAK. Training and inter-rater reliability testing were conducted with a satisfactory inter-rater reliability. Before inclusion, eligible patients were interviewed by the investigator using the Calgary Depression Scale for Schizophrenia (CDSS) [28] and the PANSS. The CDSS has been specifically developed to assess the level of depressive symptoms in schizophrenia. Depression rating scales frequently used in mood disorders may not sufficiently distinguish depressive symptoms from positive, negative and extrapyramidal symptoms in psychosis. The CDSS consists of 9 items, each giving a score of 0 to 3 points. The total CDSS sum score range is 0 to 27. A CDSS sum score > 6 has a specificity of 82% and a sensitivity of 85% for predicting a major depressive episode [29]. We used a cut-off of > 6 and ≤ 6 in correspondence with the guidelines from the authors of the CDSS [29]. The PANSS Depression Factor (PANSS-D) is the combined score of items G1 (somatic concerns), G2 (anxiety), G3 (guilt feelings), and G6 (depression) of the general psychopathology part of the PANSS. Each item is scored from 1 to 7, giving a total PANSS-D score ranging from 4 to 28. Several previous articles have performed factor analyses on the PANSS and described the PANSS-D as a measure of depressive symptoms in psychotic patients [30-32]. In the literature PANSS-D is also referred to as the Composite PANSS Depression Factor, PANSS Anxio-Depressive Dimension or PANSS Depression Subscale. Cognitive functioning at baseline was assessed by means of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [33], shown to be highly sensitive to the neurocognitive impairments associated with schizophrenia [34,35]. Misuse or dependence was reported according to Mueser et al [36].

At discharge from the hospital or at 6 weeks if not discharged, the tests and examinations were repeated by a rater who was unaware of the treatment. Serum level measurements of the antipsychotics were conducted. Thus far, all investigations and tests were part of the hospital's routine for the management of patients suffering from psychosis and became part of the patient's medical record. At this point, the patients were asked for informed consent to be contacted and included in the follow-up project.

At follow-up visits 3, 6, 12 and 24 months after baseline, measures of psychopathology were repeated by a rater blind to treatment. At each visit, all medications were recorded and the mean antipsychotic drug doses were calculated. Antipsychotic drug doses for accepted sporadic use of antipsychotics, other than the SGAs under investigation, were converted to chlorpromazine equivalent doses [37]. In cases where chlorpromazine equivalent doses could not be found in the literature, this was done by conversion to defined daily doses (DDDs) as developed by the World Health Organization Collaborating Centre for Drug Statistics Methodology [38]. The basic definition of the DDD unit is the assumed average maintenance dose per day for a drug used for its main indication in adults.

Statistical procedures

The primary analyses were intention-to-treat (ITT) analyses based on the randomization groups (RGs). That is, trial participants were analyzed in the group to which they were randomized regardless of which treatment they actually received, or how much treatment they received [39]. Secondary analyses were based on first choice groups (FCGs). Baseline data were analyzed using SPSS software (version 17.0) and by means of exact χ^2 tests for categorical data and one-way ANOVAs for continuous data. For baseline comparisons between those lost to follow-up before retesting and those who were retested, independent samples T-tests were used for continuous data and exact χ^2 tests for categorical data.

Change of depressive symptoms was analyzed in R by means of linear mixed effects (LME) models [40,41]. Fixed effects, i.e. systematic differences between the drugs, were different linear slopes in the four treatment groups, technically a group-by-time interaction with no baseline group differences. The model calculates overall

change per time unit from a common starting point for the variables in the follow-up period. This can be visually represented by the slope of a linear curve with time on the horizontal axis and the respective variable on the vertical axis. Since the aim of the present study was to investigate the overall change during the follow-up period, the LME model was considered to be the analysis of choice for this purpose. The model uses all available data and handles different numbers of visits, as well as differences in times between visits, by individual patients. Furthermore, the mixed effects model has demonstrated superior statistical power when the missing data is moderately non-ignorable [42]. For multiple comparisons, Benjamini-Hochberg adjustments were applied.

The CDSS and the PANSS are primarily developed to assess patients with schizophrenia. As the sample is diagnostically heterogeneous, a Spearman correlation analysis was performed using the SPSS software (version 17.0) to determine the consistency across the CDSS and the PANSS-D. The level of statistical significance was set at $\alpha = 0.05$, two-sided.

Power estimations were conducted in R by means of LME models. The initial CDSS sum score and within-person-variation were based on the results of a previous model [24]. CDSS sum score reductions of 10%, 20%, 50% and 70% in the respective drug groups were considered to be clinically significant differences and the corresponding slopes were entered into the model. For comparison, the EUFEST study reported a 65% overall reduction of the CDSS sum score at 12 months [15]. The initial CDSS sum score was set at 5.7 points in the model and an estimated drop-out rate of 3% per month was used. For each level of power 10,000 simulations were run. Based on these premises for the power calculations, the trial should have 80% power to detect statistically significant differences among the drugs with 45 subjects in each treatment group, and 90% power with 55 subjects in each group.

Results

The patient enrolment is displayed in Figure 1. Baseline demographic and clinical characteristics are presented in Additional file 1. A total of 226 patients were allocated to randomized sequences of the first-line SGAs listed from 1 to 4. The SGAs listed as 1 defined the randomization groups (RGs). A total of 185 (81.9%) patients received the SGA listed as 1, whereas 40 (17.7%) received another SGA on the list. The choice of SGA was unknown for one patient. There were no differences among RGs in the fractions of patients that did not choose the SGA listed as 1. The sample represented a diverse population suffering from psychosis. Five patients were diagnosed with co-morbid major depressive disorder in addition to a primary psychotic disorder; two were in the risperidone group and one in each of the other groups.

Primary outcomes - ITT analyses based on RGs

There were no statistically significant differences in baseline demographic and clinical characteristics between the RGs, thus confirming a successful randomization. There was no difference among the groups with regards to time until discontinuation of allocated drug. There were generally no substantial differences on baseline clinical or demographic characteristics between those who were lost to follow-up before retesting and those who were retested, with the exception of a slightly higher PANSS negative sub-score for those lost to follow-up (20.8 vs. 18.5 points (independent samples T-Test: $p = 0.02$; mean difference 2.3 points; 95% confidence interval (CI) 0.4-4.2)). The mean CDSS sum score at baseline was 6.4 points, varying between 0 to 23 points. The mean baseline PANSS-D sum score was 10.8 points, varying between 4 to 22 points. A total of 96 (42.7%) of the patients had a CDSS sum score > 6 points. The CDSS sum score and PANSS-D score correlated significantly (Spearman correlation coefficient $r = 0.77$; $p < 0.01$) (Figure 2). The symptom outcomes quantified by the CDSS and the PANSS-D are presented in Table 1. There was a significant time-effect showing a steady decline in depressive symptoms in all medication groups (Figures 3 and 4). Pair-wise comparisons demonstrated no statistically significant differences between the RGs on the primary outcomes. Analyses restricted to the first 90 days revealed no substantial differences among the SGAs. When affective psychoses and substance-induced psychoses, respectively, were excluded in sensitivity analyses for the whole follow-up, essentially the same results were revealed. In separate analyses in the groups with CDSS sum score > 6 or ≤ 6, respectively, there were no statistically significant differences between the SGAs. In sub-analyses on single CDSS items there were no statistically significant differences among the SGAs, except for item 8 (suicidality), as the risperidone group had a steeper daily reduction of the score compared to the olanzapine group (LME: $p = 0.031$). Corrected for multiple comparisons, this difference was no longer statistically significant (LME: $p = 0.187$). There were no statistically significant differences among the SGAs concerning anti-depressive effectiveness on the PANSS item G6 (depression).

Secondary outcomes based on FCGs

There were generally no substantial differences among FCGs on baseline demographic and clinical characteristics, with the exception of a slightly higher PANSS positive sub-score for olanzapine (21.6 points) compared with risperidone (18.4 points) (one-way ANOVA: $p < 0.001$; mean

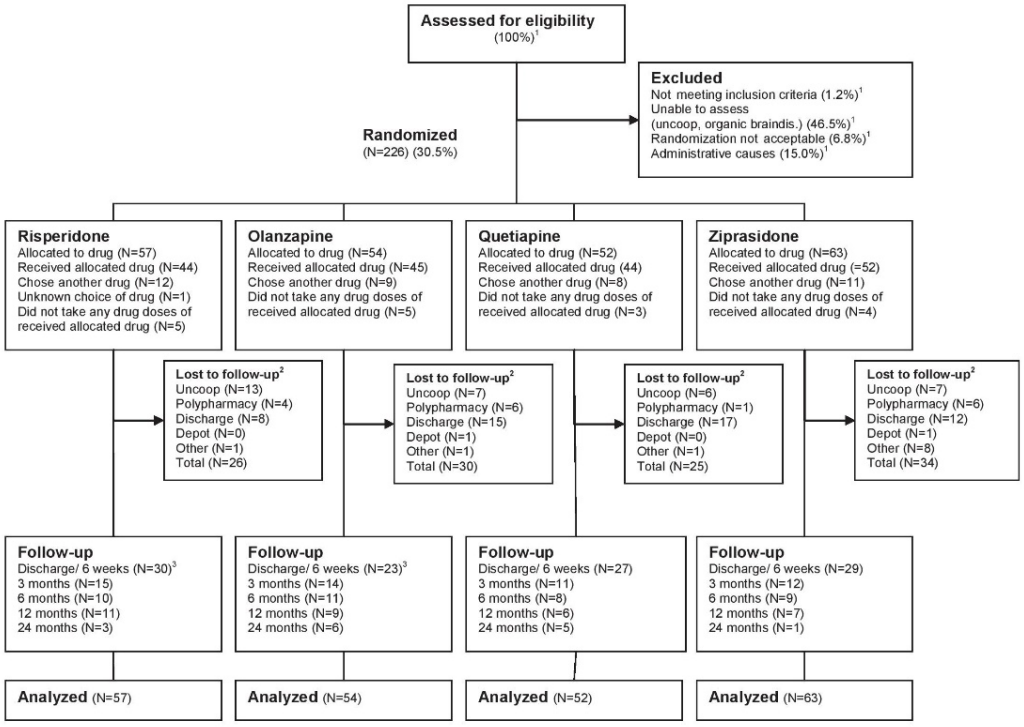

Figure 1 Flow of patients through the study. Not meeting inclusion criteria = score below 4 on all the items: delusions, hallucinatory behaviour, grandiosity, suspiciousness/persecution or unusual thought content in the Positive and Negative Syndrome Scale (PANSS); Uncoop. = the patient was not able or willing to cooperate with testing and assessments; Organic braindis. = Organic brain disorder, principally dementia; Randomization not acceptable = patient or treating clinician not willing to change existing antipsychotic medication; Administrative causes = principally patient discharged before assessments could be made. [1] Enrolment started March 2003 until 2008, week 26. Full details on enrolment were only registered from 2006, week 31 until 2008, week 26. Consequently only percentages are displayed for patients assessed for eligibility and excluded patients. [2] Before discharge/6 weeks. [3] One patient in the risperidone and olanzapine groups missed the first follow-up visit, but was retested on later visits.

difference 3.2 points; 95% CI 1.1-5.3) and ziprasidone (19.2 points) (one-way ANOVA: p = 0.011; mean difference 2.5 points; 95% CI 0.4-4.5). The mean doses in milligrams per day with standard deviations (SD) were 14.5 (5.0) for olanzapine-, 339.3 (193.4) for quetiapine-, 3.3 (1.1) for risperidone- and 100.3 (42.2) for ziprasidone-treated groups. The mean serum levels in nanomoles per liter with SD were 100.4 (72.4) for olanzapine, 398.2 (510.2) for quetiapine, 81.4 (58.3) for risperidone and 122.9 (91.3) for ziprasidone. The reference ranges were 30-200, 100-800, 30-120, and 30-200 for olanzapine, quetiapine, risperidone and ziprasidone, respectively. Data concerning psychotropic treatment was analyzed for the 108 patients who were available for retesting at discharge or at 6 weeks. A total of 30 (26.5%) patients changed their first-chosen SGA during follow-up. There were no differences among the FCGs in the frequency of change or choice of new antipsychotic drug. One or more doses of low-potency first-generation antipsychotics were given to 16 patients (14.8%). There were no differences among the FCGs in the number of patients receiving additional antipsychotics or the mean daily additional antipsychotic dose in chlorpromazine equivalents. 80 (74.1%), 28 (25.9%) and 7 (6.5%) patients received additional benzodiazepines, antidepressants and mood stabilizers, respectively. In 35 (32.4%) of these patients 2 or more of the additional psychotropics were used in combination. There were no differences among FCGs in the use of these additional psychotropics. Anticholinergics were prescribed for 6 (23.1%) of risperidone-treated FCGs. The corresponding figures were 1 (3.4%) for olanzapine-, 0 for quetiapine- and 5 (18.5%) for ziprasidone-treated FCGs (exact χ^2 test: p = 0.009). There were

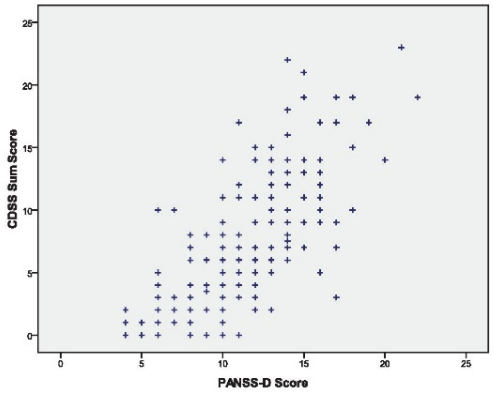

Figure 2 Correlation between CDSS sum score and PANSS-D-score at baseline. CDSS = the Calgary Depression Scale for Schizophrenia; PANSS = the Positive and Negative Syndrome Scale; PANSS-D score = PANSS Depression factor = sum score of items G1-G3 and G6 in the general psychopathology subscale of the PANSS.

no differences among FCGs in the frequency of antipsychotic drug use the year prior to index hospitalization.

The PANSS-D and CDSS scores of the primary analyses were essentially unaltered in the secondary analyses. This also applied to the sensitivity analysis restricted to the first 90 days, and to the period of actual intake of the first chosen antipsychotic drug.

Discussion

The primary aim of the present study was to investigate whether differential anti-depressive effectiveness is present among olanzapine, quetiapine, risperidone and ziprasidone in a clinically relevant sample of patients acutely admitted to hospital for symptoms of psychosis. The study was funded independently of the pharmaceutical industry and the patients were followed for up to 2 years during everyday clinical circumstances. This strengthens the applicability of the results to acutely admitted patients with psychosis in general.

There were no substantial differences among the SGAs on the primary outcome measure. The results are in line with those of the recently published EUFEST and CATIE effectiveness studies that included schizophrenia patients in first episode and chronic phase, respectively [15,16]. The collected evidence from naturalistic studies in psychosis thus indicates that if differential anti-depressive effectiveness exists among the drugs, this is likely to be of only marginal magnitude in clinical practice. As the sample was diagnostically heterogeneous the primary outcome was measured by two different inventories: the PANSS-D and the CDSS. The correlation between the sum scores of the inventories was good, but left substantial variance unexplained, thus underlining the rationale

Table 1 Numerical results of the CDSS and the PANSS-D

Outcome Measures - Change/Day	Risperidone (N = 57)	Olanzapine (N = 54)	Quetiapine (N = 52)	Ziprasidone (N = 63)
CDSS item 1 Depression	-0.0016	-0.0011	-0.0017	-0.0022
CDSS item 2 Hopelessness	-0.0010	-0.0002	-0.0005	-0.0008
CDSS item 3 Self depreciation	0.0083	-0.0002	-0.0005	-0.0006
CDSS item 4 Guilty ideas of reference	-0.0005	-0.0007	-0.0006	-0.0011
CDSS item 5 Pathological guilt	-0.0010	-0.0052	-0.0004	-0.0011
CDSS item 6 Morning depression	-0.0011	-0.0006	-0.0005	-0.0009
CDSS item 7 Early awakening	-0.0009	-0.0002	-0.0003	-0.0003
CDSS item 8 Suicide	-0.0011	-0.0002	-0.0004	-0.0006
CDSS item 9 Observed depression	-0.0008	-0.0001	-0.0004	-0.0006
CDSS sum score	-0.0093	-0.0033	-0.0048	-0.0080
PANSS item G6: Depression	-0.0015	-0.0020	-0.0027	-0.0023
PANSS-D score	-0.0014	-0.0012	-0.0014	-0.0018

N = Number of Patients; Change/Day = Mean Change of Outcome Measure per Day; CDSS = The Calgary Depression Scale for Schizophrenia. PANSS = The Positive And Negative Syndrome Scale for Schizophrenia. PANSS-D = The sum score of items G1-G3 + G6 of the General Psychopathology subscale of the PANSS.

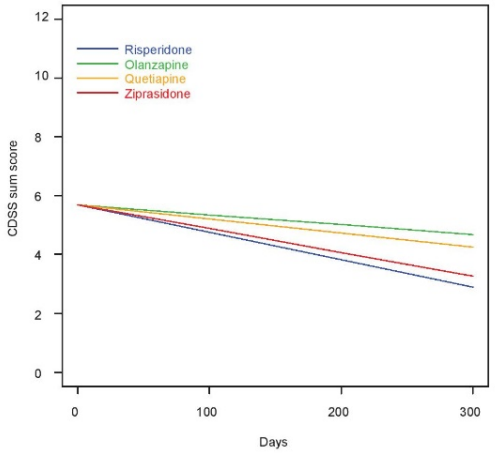

Figure 3 Change of CDSS sum score. Linear mixed effects model curves. Linear slopes for the randomization groups generated based on linear mixed effects models, CDSS sum score output, as displayed in Table 1 for olanzapine, quetiapine, risperidone and ziprasidone, respectively. The curves are confined to the first 300 days because the major bulk of data is obtained before 300 days. CDSS = the Calgary Depression Scale for Schizophrenia.

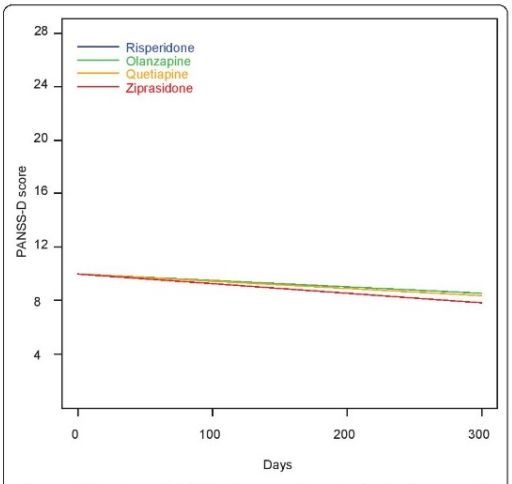

Figure 4 Change of PANSS-D score. Linear mixed effects model curves. Linear slopes for the randomization groups generated based on linear mixed effects models, PANSS-D score output, as displayed in Table 1 for olanzapine, quetiapine, risperidone and ziprasidone, respectively. The curves are confined to the first 300 days because the major bulk of data is obtained before 300 days. PANSS = The Positive and Negative Syndrome Scale; PANSS-D = PANSS Depression Factor = sum score of items G1-G3 and G6 in the general psychopathology subscale of the PANSS.

for using both inventories in the present study. The majority of prior studies indicating anti-depressive differences among antipsychotics are short term [17,19,21,43]. If the anti-depressive effects of the drugs occur mainly within the first weeks to months of treatment, differential effectiveness may, in theory, be blurred in a longer time frame. Based on the sensitivity analyses restricted to the first 90 days of follow-up our data do not support this hypothesis. Consistent with our findings there was a significant overall decrease of the CDSS score in the CATIE study. Neither study had a placebo arm, which makes interpretation of this result difficult with regards to assessing the anti-depressive effectiveness of the drugs.

Depression is highly prevalent in first-episode and acute phase psychosis [44,45]. The mean CDSS sum score in the BPP at baseline was 6.5. The CDSS sum score was > 6 for 42.7% of the sample. DeNayer et al. [21], using the same CDSS-score cut-off as in our study, found significant reductions both in the groups with CDSS sum scores > 6 and ≤6 points, respectively. Our analyses demonstrated no statistically significant differences among the SGAs in either group based on this subdivision. The equal anti-depressive effectiveness found also in the group with CDSS sum score > 6, supports our main findings. Caution should be given to the fact that subgroup analyses increase the risk of statistical type II errors. In the CATIE study quetiapine was found to be superior to risperidone in patients with a CDSS score ≥6 [16]. However, the more depressed group became relatively larger in the CATIE-trial as a consequence of the lower cut-off (CDSS ≥ 6) for depression.

The sample was diagnostically heterogeneous, though with equal diagnostic distribution among the RGs. Hypothetically, different diagnostic groups could differ in anti-depressive susceptibility from the SGAs, which could blur the overall picture. We therefore conducted sensitivity analyses, excluding the affective psychoses and substance-induced psychoses which did not skew the results. The proportion of primary affective disorders was rather low.

Some limitations apply to the study. In a moderately sized clinical trial like the Bergen Psychosis Project, the possibility of a type II statistical error exists. The BPP has, however, proven statistically powerful enough to disclose differences among the SGAs on several outcomes [24]. Furthermore, power analyses indicate that the study should have a sufficient number of subjects to detect clinically significant differences in anti-depressive effectiveness among the drugs, if present. The pragmatic design was chosen to address issues relevant to everyday clinical practice. The resulting heterogeneous sample does not have enough power to conclude statistically inside particular diagnostic subgroups. The randomization procedure allowing the patient or clinician to choose a different drug

than the first one could potentially introduce bias if there were differences among the groups in the proportions accepting the first SGA on the list. No such differences were unveiled. Furthermore, the primary analyses were intention to treat analyses based on the randomization groups. It could be argued given the naturalistic design of the study, with assessments not restricted to the time frame of actual use of the first SGA, that the outcomes may not be related to that particular SGA, but to subsequent medications. We have, however, demonstrated that about three-quarters of the patients did not change their original SGA. Moreover, there were no differences among groups in the rate of antipsychotic medication changes or the choice of a new antipsychotic agent for those who did change. Furthermore, time until discontinuation was generally the same for all SGAs. Finally, the analyses restricted to the period of actual use of first chosen drug revealed generally the same results as the primary analyses. Inherent to the pragmatic design which permits the use of concomitant psychotropics, the net effects of the SGAs under investigation may be somewhat blurred by effects of the concomitant psychotropics. The randomization was open to the patient and the treating clinician in order to imitate a clinically realistic setting. This could have introduced bias if some of the SGAs were more popular among the clinicians or patients. There was a high attrition rate, although not significantly different between the randomization groups. To our best knowledge this is a major problem in all clinical antipsychotic drug trials. Leucht and collaborators [46] state in their methodology paper that even in short-term trials of only 4 to 10 weeks more than 40% of participants discontinue prematurely. Given the long follow-up of our study we expected a high drop-out rate. This was the main reason for the choice of the mixed-effects statistical method applied, as this method is one of the preferred ones in such a situation. Reasons for drop-out were not recorded and the possibility that the more depressed patients dropped out cannot be ruled out. Still, comparisons on baseline characteristics between those with long term follow-ups and the ones leaving the study early, do not point to substantial clinical differences among the groups. Of those assessed for eligibility, only 30% were included in the trial. Theoretically, including only a fraction of eligible participants could limit the applicability of the results to the whole population. On the other hand, other clinical trials studying antipsychotics included only between 7-14% [47]. The diagnoses were determined by psychiatrists or specialists in clinical psychology, and structured clinical interviews were not systematically used, which may decrease the validity and reliability of the diagnoses. The ITT-analyses may lead to an underestimation of treatment effect. However, the substantially equal results of the ITT- and FCG-analyses indicate that this was not the case in this trial. Analyses involving single items in the CDSS should be interpreted with caution as the data are unlikely to be normally distributed. Finally, the CDSS-instrument is designed to measure depressive symptoms in schizophrenia specifically. Our sample was diagnostically heterogeneous. Somewhat surprisingly, considering that few trials indicate a superior antipsychotic effectiveness of quetiapine [15,48,49], the recently published results of the Bergen Psychosis Project demonstrated a significant superiority of quetiapine compared with olanzapine and risperidone on several psychometric scales. The present study shows that the superiority of quetiapine could not be explained by a stronger antidepressive effect.

Conclusions

In conclusion, the results of this study demonstrate no substantial differences in anti-depressive effectiveness between olanzapine, quetiapine, risperidone and ziprasidone in a clinically relevant sample of psychotic patients with moderate depressive symptoms. Based on our findings we can make no recommendations concerning choice of any particular SGA for targeting symptoms of depression in a patient acutely admitted with psychosis.

Additional material

Additional file 1: Demographic and clinical characteristics at baseline. This table displays baseline comparisons of demographic characteristics, clinical characteristics (drug- and alcohol-use, diagnoses, antipsychotic-naïve) and baseline psychometric results between the randomization groups.

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Authors' contributions

EK drafted the manuscript and participated in the statistical analyses. EJ helped to draft the manuscript, provided statistical analyses and performed the main part of the data collection. EML, RAK and HAJ helped to draft the manuscript and participated in the data collection. All authors read and approved the final manuscript.

Competing interests

Funding of the project was initiated by the Research Council of Norway, followed by Haukeland University Hospital, Division of Psychiatry. The supporters had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review or approval of the manuscript.

Kjelby E has been reimbursed by Bristol-Myers Squibb, Novartis, Lundbeck, Eli Lilly and AstraZeneca pharmaceutical companies for attending conferences.
Jørgensen HA has received honoraria for lectures given in meetings arranged by AstraZeneca and Eli Lilly.
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Løberg EM has no competing interests to declare.
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Errata for
Depressive symptoms in psychotic disorders:

Trajectories of depression and antidepressive effectiveness of antipsychotic medication

Eirik Kjelby

Thesis for the degree philosophiae doctor (PhD)

at the University of Bergen

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(date and sign. of candidate) (date and sign. of faculty)

Errata

Page 32 Misspelling: “bases” – corrected to “based”

Page 49 Misspelling “depresses” – corrected to “depressed”

Page 56 Changed word “Norwegian” – corrected to “native language”

Page 65 Changed word “dissertation” – corrected to “thesis”

Page 67 Misspelling “collections” – corrected to “collection”

Page 85 Commas missing “In correspondence with our finding of a reduced insight in the group with low depressive symptoms as accounted for in the introduction several former publications have shown” – corrected to “In correspondence with our finding of a reduced insight in the group with low depressive symptoms, as accounted for in the introduction, several former publications have shown”

Page 96 Duplicated part of sentence “… in order to more solidly conclude with the reason for drop-out and reason for drop-out.” – corrected to “… in order to more solidly conclude with the reason for drop-out.”

Page 103 Excessive space before comma “systematically will exclude a substantial proportion of the most gravely ill psychotic participants , thus leaving a gap...” – corrected to “systematically will exclude a substantial proportion of the most gravely ill psychotic participants, thus leaving a gap...”

Page 106 Wrong description “regarding drop-out 33 participants attended the 12 month visit compared to 157 in the actual data,” – corrected to “regarding drop-out 33 participants attended the 12 month visit compared to 157 in the assumed drop-out (power-analysis),”

Page 20 of paper 3 Missing word “indicating more treatment failures, possibly contributing a smaller probability of symptom-improvement.” – corrected to “indicating more treatment failures, possibly contributing to a smaller probability of symptom-improvement.”

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