Patients with anxiety and/or depression co-occurring with substance use disorders in psychiatric outpatient clinics

Detection of co-occurring substance use disorders, patient characteristics and the effectiveness of integrated treatment

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“A good head and a good heart are always a formidable combination”

Nelson Mandela

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Linda

Abbreviations

ASI	Addiction Severity Index
AUDIT	Alcohol Use Disorder Identification Test
AUS	Alcohol Use Scale
CI	Confidence Interval
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DUDIT	Drug Use Disorder Identification Test
DUS	Drug Use Scale
EuropASI	Addiction Severity Index, European version
GEE	Generalized Estimated Equations analyses
HoNOS	Health of the Nation Outcome Scales
ICC	Intraclass Correlation Coefficients
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th edition
NPR	Norwegian Patient Register
OR	Odds Ratio
RCT	Randomized Controlled Trial
PRISM	Psychiatric Research Interview for Substance and Mental disorders
SATS-r	Substance Abuse Treatment Scale revised
SCID-I	Structured Clinical Interview for DSM-IV, axis 1 disorders
SCID-II	Structured Clinical Interview for DSM-IV, axis 2 disorders
SCL-90r	Symptom Check List 90 items revised
SPSS	Statistical Package for the Social Sciences

Preface

My interest in patients with co-occurring mental health and substance use disorders started when I was working as a junior registrar / resident specializing in psychiatry on an inpatient ward for patients with chronic psychotic disorders from 2003 to 2004 (Vor Frue Hospital). Just a couple of years earlier the patient group of this hospital was dominated by older schizophrenic patients with no substance abuse and long-term treatment on the ward. By 2003, the patient group was dominated by younger patients with schizophrenia co-occurring with substance use disorders. At the same time, increasing demands for effectiveness had shortened the average patient stay on the ward from years to months. The hospital is located in the centre of Oslo where illegal substances are easily available. Several of these young patients liked using drugs for a variety of reasons: it was a form of opposition towards authority (adults in general and treatment providers like myself, specifically); it seemed to be a way of creating an identity in a subgroup of "equals"; and it seemed that many of them liked the feeling of balancing on the edge of psychosis. This made it difficult to establish a common understanding with patients about the harmfulness of the drug use and the fact that the drugs exacerbated the recurring bizarre and devastating psychotic episodes that only made them sicker each time. This necessitated involuntary treatment which, in turn, increased their despite of authority and made it even more difficult to establish a rapport and a shared understanding of the problem and its possible solutions. For me, as a treatment provider, this was extremely difficult to watch. In addition, as this change in the patient group had happened over a short time, the staff did not have the skills to meet the challenges or to provide treatment approaches tailored to this group of patients.

A few years later, I was able to take part in a supervision group for doctors working with patients with substance use disorders led by Professor Helge Waal. He was interested in recruiting physicians into research, and when he announced that a PhD fellowship concerning the effectiveness of integrated treatment for co-occurring mental disorders and substance use disorders in psychiatric outpatient clinics was available, I gladly applied.

The project was initiated and led by Rolf Gråwe, a senior researcher at Sintef Health Research at the time. It was organized as a consortium between the Regional Centre for Co-occurring Disorders of Substance Abuse and Mental Health (represented by Amund Aakerholt), the Centre of Competence for Addiction Issues – Region East (represented by Helge Haugerud), the Norwegian Centre for

Addiction Research at the University of Oslo (represented by Helge Waal), and Sintef Health Research (represented by Rolf Gråwe). By the time I came into the project, the funding was established and the participating community mental health centres were recruited. We continued with writing and revising the treatment manual, engaging local trial administrators and therapists and teaching them how to run the project and assess and treat patients. This study and its results are described in papers III and IV.

To complement our treatment study with an epidemiological point of view, we looked at data from a study of the development of community mental health centres (including psychiatric outpatient clinics) as part of the evaluation of the National Plan for Mental Health between 2002 and 2007. This project had been led and conducted by Rolf Gråwe and Torleif Ruud, both working at Sintef Health Research at the time. We found this material useful in regard to studying patient characteristics and treatment outcomes for psychiatric outpatients with co-occurring substance use disorders compared to psychiatric outpatients without this comorbidity. This study and its results are described in papers I and II.

Summary

Background:

Increasing evidence shows that substance use disorders and psychiatric illness often co-occur, and that this co-morbidity renders treatment more difficult and results in greater use of health services. However, such studies have primarily focused on inpatient populations dominated by psychotic disorders, whereas our studies investigate patients in community mental health centres where affective and anxiety disorders are more prominent.

Aims:

The overall aims were: 1) to examine if patients with co-occurring mental disorders and substance use disorders were detected in psychiatric outpatient clinics and if they differed from outpatients without substance use disorders (papers I and II). 2) to investigate whether integrated treatment, which has been shown to be effective for inpatients with substance use disorders co-occurring with severe mental disorders, is as effective in outpatients with substance use disorders co-occurring with less severe mental disorders like anxiety and depression (papers III and IV).

Material and methods:

This thesis consists of two studies. The first study was a cross-sectional study that used a subset of data from an evaluation of the National Plan for Mental Health. All patients seen in eight community mental health centres during a 4-week period in 2007 were studied. The number of included patients was 2154. The centres were located in both rural and urban areas of Norway. The patients were diagnosed according to the ICD-10 diagnoses and assessed with the Health of the Nation Outcome Scales, the Alcohol Use Scale, and the Drug Use Scale.

Our second study was a pragmatic group randomized clinical trial comparing the effectiveness of integrated treatment to treatment as usual in community mental health centres. Five centres were drawn to the intervention group and four to the control group. The allocation to treatment conditions was not blinded. New referrals were screened with the Alcohol Use Disorder Identification Test (AUDIT) and the Drug Use Disorder Identification Test (DUDIT). Those who scored above the cut-off level of these instruments were assessed with the Structured Clinical Interview for DSM-IV 1 and 2. We included patients with anxiety and/or depression together with one or more substance use

disorders. The outcome measures were the AUDIT, the DUDIT, the European version of the Addiction Severity Index, the Symptom Check List-90r, and the Substance Abuse Treatment Scale. We included 55 patients in the intervention group and 21 in the control group. We used a linear multi-level model.

Results:

According to our first study, all the different measures used gave low prevalence rates of substance use disorders, and the inter-measure agreement was poor. A combination of the measures gave prevalence rates closer to what would be expected on the basis of previous epidemiological studies. Further, the patients with substance use disorders in community mental health centres were more frequently male, single and living alone, had more severe morbidity, less anxiety and mood disorders, less outpatient treatment and less improvement with regard to recovery from psychological symptoms compared to patients with no substance use disorder.

According to our second study, both the intervention group and the control group reduced their alcohol and substance use during the trial, but there was no change in psychiatric symptoms in either group. However, the intervention group had a greater increase in motivation for substance use treatment after 12 months than the control group. There were no adverse events.

Conclusion:

The community mental health centres participating in this study lacked sufficient diagnostic routines and instruments to identify substance use disorders. Clinical research that relies on the methods used in this study will need combined approaches to provide reliable findings. Patients with co-occurring mental and substance use disorders in community mental health centres differ from patients without this comorbidity. Consequently, community mental health centres need to implement systematic screening and diagnostic procedures in order to detect the special needs of these patients and improve their treatment. Both clinical practice and research would benefit from valid, reliable screening methods and diagnostic procedures.

Integrated treatment is effective in increasing the motivation for treatment among patients with anxiety and/or depression co-occurring with substance use disorders in outpatient clinics. Studies of complex interventions in unselected clinical populations are essential in the development of evidence-based treatments in the psychiatric and addiction field. The methodological problems of

such studies are considerable but possible to overcome by thorough planning and by addressing the obstacles at an early stage.

Sammendrag (Norwegian)

Bakgrunn:

Epidemiologiske og kliniske studier har gjennom en årrekke vist at det er stor samsykelighet mellom ruslidelser og psykiske lidelser, at denne samsykeligheten gjør behandlingen vanskeligere og at den resulterer i lengre sykdomsforløp og større forbruk av helsetjenester. Imidlertid har tidligere studier hovedsakelig undersøkt innlagte pasienter i sykehus med alvorlige psykiske lidelser, som psykoselidelser, sammen med ruslidelser. I våre studier har vi undersøkt pasienter i psykiatriske poliklinikker der lettere psykiske lidelser som angst og depresjon er mer vanlig.

Formål:

De overordnede formålene med studiene var: 1) å undersøke om pasienter med ruslidelse og psykiske lidelser blir fanget opp i psykiatriske poliklinikker og om disse pasientene skiller seg fra pasienter uten slik samsykelighet (artikkel I og II). 2) å undersøke om Integrert Behandling, som har vist seg å være effektiv i behandling av inneliggende pasienter med alvorlig psykisk lidelse sammen med ruslidelse, også er effektiv for å behandle polikliniske pasienter med lettere psykiske lidelser slik som angst og depresjon sammen med ruslidelse (artikkel III og IV).

Materiale og metode:

Dette doktorgradsarbeidet består av to studier. Vår første studie var en tverrsnittsstudie der vi gjorde bruk av data fra evalueringen av Opptrappingsplanen for Psykisk Helse. Alle pasienter som mottok behandling i åtte Distriktspsykiatriske sentre (DPS) i løpet av en 4 ukers periode i 2007 ble undersøkt, og 2154 pasienter ble inkludert i studien. DPS'ene var lokalisert i både urbane og rurale strøk i Norge. Pasientene ble diagnostisert i henhold til det internasjonale klassifikasjonssystemet for diagnoser (ICD-10) og undersøkt med Health of the Nation Outcome Scales, Alcohol Use Scale og Drug Use Scale.

Vår andre studie var en pragmatisk, grupperandomisert, klinisk studie som sammenliknet effekten av Integrert Behandling med standard behandling i ni DPS. Fem DPS ble trukket til behandlingsgruppen og fire til kontrollgruppen. Gruppefordelingen var ikke blindet. Nyhenviste pasienter ble screenet for problematisk bruk av alkohol og andre rusmidler med Alcohol Use Identification Test (AUDIT) og Drug Use Identification Test (DUDIT). De som skåret over grensen for problematisk bruk ble intervjuet med

diagnoseverktøyene SCID1 og 2. Pasienter som fikk påvist angst- og / eller depressiv lidelse sammen med ruslidelse ble inkludert i studien ved samtykke. Pasientene ble fulgt og undersøkt etter 6 og 12 måneder med henblikk på endring i rusbruk, psykiske symptomer og motivasjon for endring av rusbruk. Instrumentene som ble brukt til dette var AUDIT, DUDIT, den europeiske versjonen av Addiction Severity Index, Symptom Check-List 90r og Substance Abuse Treatment Scale. Femtifem pasienter ble inkludert til intervensjonsgruppen og 21 til kontrollgruppen. Vi brukte en lineær, hierarkisk modell til de statistiske analysene.

Resultater:

I følge vår første studie viste alle måleinstrumentene som ble brukt en lavere forekomst av ruslidelse blant pasientene enn det som var forventet fra andre studier. I tillegg var det dårlig samsvar mellom forekomstene målt med de ulike instrumentene. Da vi kombinerte disse instrumentene nærmet forekomsttallet seg det som var forventet. Videre viste studien at pasientene med ruslidelse oftere var menn, enslige og at de bodde alene. I tillegg hadde de alvorligere sykelighet, mindre forekomst av angst og stemningslidelser, mindre poliklinisk behandling og mindre grad av bedring fra psykologiske symptomer enn pasienter uten ruslidelse.

I følge vår andre studie, reduserte begge gruppene sitt alkohol- og rusbruk i løpet av undersøkelsen, men ingen av gruppene fikk noen endring i psykiske symptomer. Intervensjonsgruppen økte imidlertid sin motivasjon for å redusere sitt rusbruk i større grad enn kontrollgruppen. Det forekom ingen uheldige hendelser som følge av studien.

Konklusjon:

DPS'ene som deltok i vår første studie manglet diagnostiske rutiner for å fange opp ruslidelse hos pasientene sine. Kliniske studier som baserer seg på måleinstrumentene som ble brukt i denne studien må kombinere disse for å være sikre på å fange opp pasienter med problematisk rusbruk. Videre skiller pasienter med ruslidelse i psykiatriske poliklinikker seg fra de uten ruslidelse på områder som vil påvirke grad av sykelighet og behandlingsrespons. Dette betyr at DPS'ene må innføre rutiner for å fange opp disse pasientene slik at behandlingen blir tilpasset deres behov og behandlingsresponsen bedres. Både klinisk praksis og forskning vil nyte godt av å gjøre bruk av valide og pålitelige screeningmetoder og diagnostiske prosedyrer.

Integrert behandling er effektiv i å øke motivasjonen for behandling hos polikliniske pasienter med angst og/ eller depresjon sammen med ruslidelse. Behandling av pasienter med sammensatte lidelser krever komplekse intervensjoner, men studier av komplekse intervensjoner og pasienter med sammensatte lidelser er krevende og metodisk utfordrende. For å utvikle effektive behandlingsformer for denne gruppen pasienter, er det likevel viktig at slike studier blir gjennomført. Vår studie viser at til tross for metodiske vanskeligheter, vil det med god planlegging være mulig å gjennomføre slike studier.

List of papers

I

Wusthoff, L. E., Waal, H., Ruud, T., Roislien, J., & Grawe, R. W. Identifying co-occurring substance use disorders in community mental health centres. Tailored approaches are needed. *Nordic Journal of Psychiatry. 2011, 65*(1), 58-64. doi: 10.3109/08039488.2010.489954. Epub 2010 May 28.

II

Wusthoff, L. E., Waal, H., Ruud, T., & Grawe, R. W. A cross-sectional study of patients with and without substance use disorders in Community Mental Health Centres. *BMC Psychiatry. 2011, 11*, 93. doi: 10.1186/1471-244X-11-93.

III

Wusthoff, L. E., Waal, H., & Grawe, R. W. The effectiveness of Integrated Treatment in patients with substance use disorders co-occurring with anxiety and/or depression – a group randomized trial. *BMC Psychiatry. 2014, 14:67*. doi: 10.1186/1471-244X-14-67

IV

Wusthoff, L. E., Waal, H., & Grawe, R. W. When research meets reality - lessons learned from a pragmatic multisite group-randomized clinical trial on psychosocial interventions in the psychiatric and addiction field. *Substance Abuse: Research and Treatment. 2012, 6*, 95-106. doi: 10.4137/SART.S9245. Epub 2012.

1. Introduction – Context and terminology

1.1 Substance use disorders and mental disorders

There are two widely used classification systems for diagnoses; the Diagnostic and Statistical Manual for Mental Disorders (DSM) published by the American Psychiatric Association, and the International Classification of Diseases (ICD) published by the World Health Organization. While conducting our studies, the DSM-IV-text revision and the ICD-10 were the latest versions of these classification systems. In DSM-IV substance related disorders were categorized in two main categories; substance abuse and substance dependence, with each specific substance addressed as a separate substance related disorder (1). The distinction between abuse and dependence was based on the concept of abuse being a mild or early phase and dependence a more severe manifestation of the disorder, meaning that the former would have to precede the latter. However, it has been shown that this is not always the case. In ICD-10 a similar distinction is made between harmful use and dependence (2). Recently, an updated version of the DSM has been published; the DSM-V. In DSM-V the categories from DSM-IV, i.e. abuse and dependence, are combined into one single disorder measured on a continuum from mild to severe, i.e. a substance use disorder. In this definition, a milder form of substance use disorder does not have to precede a more severe form (3). In our studies, the term *substance use disorder* is referred to as abuse of or dependence on both alcohol and other substances.

The concept of mental disorders lacks a consistent operational definition to cover all situations. In the DSM-IV a mental disorder is defined as a clinically significant behavioural or psychological syndrome or pattern that is associated with present distress, disability or a significantly increased risk of suffering death, pain, or an important loss of freedom. Further, it must be a manifestation of a behavioural, psychological, or biological dysfunction, and not merely an expectable and culturally sanctioned response to a particular event. It should be a symptom of dysfunction in the individual and not only a deviant behaviour or conflict between the individual and the society (1, 4). Mental disorders are commonly divided into severe and less severe mental disorders. The term *severe mental disorder* refers to psychiatric disorders with a severe impact on the person's psychosocial functioning, like the ability to work, take care of one self, and maintain interpersonal relationships. Additionally, a severe mental disorder will often include psychotic symptoms such as hallucinations or delusions (5). The most common examples of such disorders are schizophrenia and bipolar disorders. *Less severe mental disorders* allude to psychiatric disorders with less impact on

psychosocial functioning and which do not include psychotic symptoms. The most common examples of such disorders are anxiety and mild to moderate depressive disorders, i.e. depression without psychotic symptoms. In our clinical trial we have included all subgroups of anxiety and mild to moderate depressive disorders.

1.2 Co-occurring mental and substance use disorders

Traditionally, the term "dual diagnosis" was used for the co-occurrence of severe mental disorders and substance use disorders (6, 7). However, "dual" refers to two co-occurring conditions, and in many instances there are more than two conditions co-occurring, e.g. one or more mental disorders together with one or more substance use disorders. Further, one can have co-occurring conditions other than mental disorders combined with substance use disorders, for example, hypertension, and diabetes. The term "dual diagnosis" is therefore not precise and by preference the term "co-occurring" is used, where one must specify which conditions co-occur in each case (6). The terms *co-occurring* and *comorbid* are used synonymously throughout our studies.

1.3 Aetiological theories on co-occurring mental and substance use disorders

There are different models which try to explain the high prevalence of co-occurring substance use disorders and mental disorders (5, 8-16). Many of these models concern the co-occurrence of severe mental disorders and substance use disorders. Merikangas et al (17, 18), propose *causal* and *shared aetiological* explanations. Similarly, a review of aetiological theories for the comorbidity between substance use disorders and severe mental disorders by Mueser et al (15) proposes four general models*; the common factor models, the secondary substance abuse disorder models, the secondary psychopathology models, and the bidirectional models*. Some of these models might also apply as aetiological explanations for the comorbidity of substance use disorders and less severe mental disorders. As our studies concern the co-occurrence of less severe mental disorders and substance use disorders, the following will comprise of the proposed aetiology of these disorders. Kushner et al (19) and Swendsen et al (20) have reviewed different models of aetiology for the co-occurrence of substance use disorders together with anxiety and depressive disorders, respectively.

Causality models are based on the presumption that one, primary, disorder precedes the other, secondary, disorder in time and that the *primary disorders*, in different ways, might cause the co-occurrence of the *secondary disorder* (21-23). There might also be a *bidirectional* causation, meaning that either disorder can increase the vulnerability to the other (15). The causal explanations might be distinguished as direct causality or indirect causality (24). *Direct causality* means that the secondary disorder might be elicited directly by the primary disorder, e.g. pharmacological effects of ethanol inducing depressive symptoms. *Indirect causality* means that the secondary disorder is caused by secondary effects of the primary disorder. An example would be the "self-medication hypothesis" (25-27), e.g. using alcohol to cope with anxiety symptoms. Additionally, there could be a development of risk factors for the comorbid disorder as a result of the primary disorder, e.g. job loss due to an alcohol use disorder could induce the onset of a depressive episode (28).

A review by Kushner et al (19) of the comorbidity of anxiety and alcohol use disorders found that the short-term anxiolytic effects of alcohol and the long-term anxiogenic effects of alcohol suggest that both anxiety disorders and alcohol use disorders can serve to initiate the other, especially in the case of alcohol dependence. Further, clinical studies suggest that: anxiety disorders can contribute to the maintenance of and relapse to alcohol abuse; that reducing anxiety symptoms improves the treatment outcome for an alcohol use disorder; and that ongoing panic and anxiety predict relapse to alcohol abuse. Altogether a vicious circle of increasing anxiety symptoms and alcohol use is produced and this promotes and sustains comorbidity (12, 19). Regarding the comorbidity of anxiety disorders and other drug use disorders, epidemiological studies support the finding that anxiety disorder precedes the substance use disorder in many cases (14, 29). Prospective studies suggest that the predictive value between anxiety and substance use disorders is bidirectional in adolescents and young adults (30, 31). There is no data to support a unilateral relationship between depression and substance use disorders. It seems that both disorders are risk factors for developing the other (28, 29).

The models of *shared aetiology* (17), also called *common factor models* (8, 15), suggest that one or more factors independently increase the risk of both the psychiatric illness and the substance use disorder. These factors could be genetic, non-biological environmental factors (e.g. disruptive family), prenatal environmental factors (e.g. maternal alcohol use), or biological environmental factors (e.g. lead-poisoning) (17).

If genetic or other familial factors were to be common contributory factors for comorbid mental and substance use disorders, one would expect relatives of people with substance use disorders to have a higher prevalence of mental disorders, and relatives of people with mental disorders to have higher prevalence of substance use disorders. Some studies suggest that there might be a causal relationship between anxiety and alcoholism as probands with either disorder alone have family members with increased risk of comorbidity (18, 32), but there does not seem to be a cross-transmission to support a common aetiology between anxiety disorders and alcoholism (19, 33). Prospective studies suggest that problems with either anxiety or alcohol use alone can promote the development of the other and that shyness and behavioural inhibition among boys in childhood predicts the development of alcohol abuse in adolescence and young adulthood (34, 35). Further, anxiety spectrum conditions in adults predict later development of alcohol use disorders (36). Regarding the comorbidity of depression and substance use disorders, twin studies provide weak support for a shared diathesis when it comes to the relationship between depression and alcoholism (28, 33, 37-39), but this is not supported by adoption studies (28, 40, 41). In addition, family studies show that substance use disorders in probands are associated with both substance use and depression among relatives (42) and that maternal depression is associated with both depression and substance use in offspring (28, 43).

1.4 Setting - Community Mental Health Centres

In 1996 the Norwegian government proposed a National Plan for Mental Health to strengthen the mental health services. The initial National Plan for Mental Health was put into action from 1999-2006 and later prolonged until 2008. It involved, among other actions, the development of community mental health centres throughout the country (44, 45). These centres provide decentralized specialist mental health services and are responsible for providing services for psychiatric emergencies, diagnostic assessments, and specialized psychiatric treatment, together with consultations and advice for collaborative service providers. They are meant to be a link between the centralized specialist health services (i.e. the hospitals) and the municipalities (46). The treatment services offered at each centre varies, but all of them have psychiatric outpatient clinics that offer individual therapy and some also provide additional group therapy. Many have a day-patient programme, and some offer short-term inpatient treatment for patients with chronic severe mental disorders (45). The evaluation of the National Plan for Mental Health showed that some patients did not receive sufficient treatment. This was especially true for patients with severe mental disorders in combination with substance use disorders, and this resulted in the development of

Assertive Community Teams. These teams are organized at the community mental health centres in close collaboration with the municipalities. The first Assertive Community Team was established in 2007, others followed from 2009 with government financing. In 2012 fourteen Assertive Community Teams were established throughout Norway (47). In 2004 the responsibility for addiction treatment was moved from the county authorities to the specialist health services as a result of the Addiction Treatment Reform ("Rusreformen") (48). This reform had many implications, for example, people seeking addiction treatment received patient rights according to Norwegian health legislation. Previously the specialist health services (including the psychiatric outpatient clinics at the community mental health centres) were responsible for treating patients where the mental disorder was the dominant need for treatment, e.g. patients with severe mental disorders co-occurring with substance use disorders. The county authorities were responsible for treating patients where the substance use disorder was the dominant need for treatment, e.g. patients with substance use disorders only or a severe substance use disorder co-occurring with a less severe mental disorder. As a consequence of the addiction treatment reform, the community mental health centres gradually developed addiction outpatient clinics in addition to their existing services.

In our studies, we have included patients from different community mental health centres throughout Norway. In our first study (papers I and II) we included patients from all the services at the community mental health centres, but as patients were predominantly receiving services from the psychiatric outpatient clinics, the terms *community mental health centres* and *psychiatric outpatient clinics* are used synonymously. In our second study (papers III and IV) we included patients from the psychiatric outpatient clinics only.

2. Background

2.1 The prevalence and characteristics of patients with co-occurring mental and substance use disorders

Since the early 1980s there has been mounting evidence of high prevalence of substance use disorders in the general population. The lifetime prevalence of any substance use disorder has been shown to range from 15% to 19% between studies (49-51) and that of alcohol abuse from 12% to 29% (29). Likewise, the twelve month prevalence of any substance use disorder ranges from 8% to 9% between studies, that for alcohol abuse or dependence ranges from 7% to 11% (50, 52-54), and the one month prevalence of any substance use disorders range between 4% and 6% (49, 50).

Epidemiological studies have also established high comorbidity between mental and substance use disorders (29, 49, 55-57), with the odds ratio for the 12 month occurrence of any substance use disorder with at least one mental disorder being 2.6 (55). In clinical populations this comorbidity is even more pronounced particularly among homeless groups (58) and in acute psychiatric wards where patients with psychotic disorders like schizophrenia are the main patient group (59, 60). The prevalence of patients with co-occurring severe mental disorders and substance use disorders in inpatient psychiatric settings varies considerably between studies, i.e. between 24-50% (59-61). This can be explained by several factors, such as, differences in the levels of substance use in the catchment area, admission policies at the wards or insufficient diagnostic practice (62). Studies have shown that diagnoses of substance use disorders are often missed in psychiatric patients (63-65). This underlines the importance of implementing good screening procedures to aid diagnostic assessments (65, 66).

When we started our study, much was known about the prevalence of patients with co-occurring severe mental illnesses and substance use disorders in psychiatric inpatient clinics. However, studies from outpatient clinics were scarce and to a large degree based on samples of patient with severe mental disorders (67). Less was known about the prevalence of co-occurring substance use disorders among patients with less severe mental disorders, like anxiety and depression, and whether their comorbidity was being detected and addressed.

From clinical studies it is evident that people with co-occurring mental and substance use disorders are more often men and less likely to be in a relationship or employed (62, 68-71), they have a low level of education, low socioeconomic status (62, 68, 71, 72) and have a higher level of mental distress (67, 70, 71). However, most of these studies are from patients in substance use treatment settings or from patients with severe mental disorders co-occurring with substance use disorders. Consequently, when we did our studies, less was known about the characteristics of patients with co-occurring mental and substance use disorders in general psychiatric outpatient clinics, for example, whether these patients differed from psychiatric outpatients without this comorbidity and if the community mental health centres differentiated their treatment accordingly.

2.2 Clinical course and treatment services

Comorbid mental and substance use disorders have long been known to be associated with poorer treatment effect resulting in poorer psychosocial functioning, a higher number of days in treatment, higher attrition from treatment, more admissions, and a higher burden for patients from both their mental and substance use disorders (73-79). Hence, this comorbidity complicates the recovery of mental health disorders and is associated with an increased use of health services (74, 80-83).

During the 1980's it became evident that existing treatment systems were a poor fit for these comorbid disorders as mental health and substance abuse services were provided in separate, parallel treatment systems. These systems had different treatment philosophies and little capacity for modifying treatment approaches or cooperating to individualize treatments. This complicated further recovery from these disorders (7). Treatment in these separate systems was commonly provided either in a sequential or parallel manner. *Sequential treatment* means that the patient is first treated for one condition at the corresponding service (e.g. treatment for a mental disorder at a psychiatric clinic) and is then treated for the other condition at the other treatment service (e.g. treatment for a substance use disorder at an addiction treatment service). There are several disadvantages to this approach: the untreated disorder might worsen the other, resulting in a disagreement about which disorder should be treated first, leaving the patient "ping-ponging" between services. It may also be unclear when one disorder has been treated sufficiently for the patient to receive treatment for the other disorder. There also is a risk that the patient is not referred for the other treatment (5). *Parallel treatment* means that the patient is treated for both the mental disorder and the substance use disorder at the same time but at different treatment sites. This can be a fruitful approach if the therapists at the different sites collaborate and the treatments are well

coordinated. However, the parallel treatment approach has often been shown to be problematic. Therapists may come from different theoretical backgrounds and provide different views on how to understand and treat the conditions. Consequently, the treatments are often poorly coordinated and, ultimately, it is up to the patient to integrate the different approaches for his/her conditions. In addition, in most cases it is difficult for services to be offered from two sites at the same time (5, 7).

To overcome these difficulties, approaches to integrate the treatments and services for patients with co-occurring mental and substance use disorders were developed during the late 1980s (7, 84, 85). The primary target group for this integrated approach was the hard-to-reach patients with severe mental disorders, like schizophrenia, and co-occurring substance use disorders. These patients were difficult to reach, usually dropped out of treatment, and had a high degree of psychosocial impairment including the ability to work, taking care of oneself, and maintaining interpersonal relationships. Many such individuals also lack a place to live and monetary income. Consequently, a large range of services is needed, e.g. somatic and psychiatric health services and social services (5). Hence, integration of services is needed on many levels; the organizational level, the treatment level, and the therapist level (5).

Knowledge about this area has grown steadily since the 1980s and the Addiction Treatment Reform was established in Norway in 2004. However, when we started our studies in 2007, treatment services for mental and substance use disorders in Norway were still predominantly divided in two parallel streams, and outreach teams for hard-to-reach patients with co-occurring severe mental and substance use disorders were still considered to be pioneering (86). Even today, ten years after the Addiction Treatment Reform, many of the services for mental health and addiction still operate in parallel systems with different philosophies and traditions that make collaboration around patients with co-occurring mental and substance use disorders difficult. In an attempt to address these problems, the Norwegian Directorate of Health, published new guidelines for treating patients with co-occurring mental and substance use disorders in 2012 that advocate closer collaboration and integration of treatment and services (87)

2.3 Integrated treatment

As described above, means to integrate the treatments and services for patients with co-occurring mental and substance use disorders were developed during the late 1980s (7, 84, 85), and clinical guidelines were later described by Minkoff (88). This *integrated treatment* has over the years

become part of treatment recommendations for patients with co-occurring severe mental and substance use disorders in several countries (87, 89, 90). Mueser et al (5) describe this integration of treatment and services as follows.

Firstly, there needs to be an *integration of services*, i.e. the patient needs to be offered treatment for both the mental and substance use disorders simultaneously from the same therapist or group of therapists within the same organization. Secondly, the services need to be *comprehensive*, i.e. a wide array of service providers needs to cooperate to avoid gaps in the services delivered. Thirdly, the services need to be *assertive* and flexible in order to reach patients who are not able to keep to specific appointments. Further, it is important to reduce negative consequences of the disorders, i.e. "*harm-reduction*", to make sure the patient lives long enough to gain the benefits from treatment; e.g. clean needles and syringes and vaccination against hepatitis A and B. As these conditions are often long-term, it is also important to have a *long-term perspective* on the treatment and services given, i.e. time-unlimited services, to avoid artificial constraints that would prematurely terminate treatment. Further, these conditions are highly dependent on the patient's ability and willingness to change his or her behaviour so the treatment needs to be *motivation based*, i.e. engaging the patient in his / her treatment, and eliciting their own motivation for change. For the same reason, the treatment should be adapted to the person's stage of change (91-93) and tailored to the specific needs of the individual (94). Finally, as this condition is highly complex, a broad array of therapeutic tools will be needed, i.e. *multiple psychotherapeutic modalities*, e.g. individual therapy, group therapy, family therapy and so forth (5, 7). Commonly used psychotherapeutic modalities are motivational interviewing (95-97) and cognitive behavioural therapy (5, 98). The combination of these modalities has also shown to be effective (99, 100).

Over the years, several studies have been published about the effectiveness of integrated treatment for people with severe mental disorders co-occurring with substance use disorders (101-110). Although individual studies show promising results, systematic reviews pooling the results have not been able to replicate these findings (99, 111-114). These reviews conclude that the heterogeneity in treatment modalities, sample characteristics and diagnostic features make pooling of effect-sizes difficult. However, one recent review concludes that, despite this heterogeneity, the integration of several treatment modalities is more effective than approaches with single treatment modalities (114). This heterogeneity among studies clearly shows that integrated treatment is not one form of treatment. Over the years, several models of integrated treatment have been developed (115). Although these treatment models differ in several ways, they share a common set of principles which

are listed by Mueser and Gingerich as follows: “taking a low-stress and harm-reduction approach, motivation-based treatment (including a stage-wise approach), use of cognitive-behavioural treatment strategies, supporting functional recovery, and engaging the individual’s social network” (115).

During recent years, different models of integrated treatment have also been developed to address a broader spectrum of comorbid illnesses including less severe mental disorders co-occurring with substance use disorders. It has become evident that comorbidity of different combinations of substance use and mental disorders need different combinations of treatment approaches (16, 116). Some studies suggest that different sequencing of the treatment modalities and thematic focus within the integrated treatment approach is of importance for different combinations of mental and substance use disorders (117, 118). Rohde et al (117) evaluated three methods of integrating interventions for depression and substance use disorders amongst adolescents. The intervention for depression was a cognitive behavioural group intervention (Adolescent Coping with Depression course) and the intervention for the substance use disorders was Functional Family Therapy. They found that intervening on the substance use disorder first had better outcomes on substance use for most of the patients. However, for patients with a major depressive disorder at baseline, intervening on depression first had better outcome on substance use disorders. Depressive symptoms decreased significantly in all treatment groups. Gender differences might also influence which disorder should be addressed first. Baker et al (119) did a randomized controlled trial among patients with alcohol use problems and depression. The participants were divided into 4 groups. All groups received one brief intervention session with an integrated focus on depression and alcohol misuse. Three of the four groups received, in addition, nine sessions with either alcohol focus, depression focus or integrated focus. The integrated focus treatment was associated with greater reduction in drinking days and level of depression compared to the single-focus treatments (just alcohol or just depression). However, when gender was taken into account, the alcohol-focused treatment was associated with greater reduction in alcohol consumption and increased level of functioning in men. In women, the depression-focused treatment was associated with greater improvement on each of these variables. This might be explained by different aetiology of the comorbidity between genders (120, 121). Schuckit et al (122) found that among alcohol-dependent patients there was a preponderance of alcohol-induced depression in men and that independent depression was most likely found in women. These findings suggest that treatment should be tailored according to gender (116).

When we started planning our treatment study in 2005/06 and initiated it in 2007, many studies had investigated the effectiveness of integrated treatment for patients with severe mental illness and substance use disorders. However, the literature was very scarce when it came to integrated treatment for people with less severe mental disorders, like anxiety and depression, and substance use disorders. In 2008, Morten Hesse carried out a systematic review of the literature on integrated psychosocial interventions for people with anxiety and/or depression co-occurring with substance use disorders and found ten studies from different treatment settings (123). Five of these were studies on psychosocial interventions for depressive disorders co-occurring with substance use disorders (124-128) and five were studies on psychosocial interventions for people with anxiety disorders co-occurring with substance use disorders (129-133). There was considerable heterogeneity among the studies with different inclusion criteria, interventions, control conditions, and outcome measures, so comparing their effect sizes was difficult. Consequently, when we started our clinical trial in 2007, little was known about the effects of integrated treatment for patients with less severe mental disorders, i.e. anxiety and depressive disorders, co-occurring with substance use disorders in psychiatric outpatient clinics where these conditions are more prominent.

2.4 Methodological issues in treatment research

To address the treatment issues mentioned above, research on effective and evidence-based treatment approaches for this group of patients is vital, and should be based on rigorous and valid research methods (134, 135). The randomized controlled trial (RCT) is considered to be the best research design to compare different treatment approaches because of its ability to maximize internal validity and thereby enable studies to attribute differential outcomes to the experimental manipulation rather than other causes (134, 136). However, this strong internal validity comes at the expense of poorer external validity, which reduces the generalizability of the results to heterogeneous groups of patients and settings that are common in everyday clinical practice (137-139).

One of the prerequisites for establishing strong internal validity is a strict manualized treatment conducted by highly trained and specialized therapists. However, in everyday clinical practice, clinicians face a wide range of disorders that require an eclectic approach tailored to meet the differential needs of the individual patient. Additionally, the clinicians that provide these treatments,

typically, come from different professional backgrounds with different experience and training (138-140).

Another feature of the RCT is the use of randomization to create groups which are equal with regard to known and unknown confounding factors. This, however, presupposes that the sample size is large enough compared to the number of variables (141). In many randomized clinical trials, difficulties in recruitment are common (142-145). Additionally, people with substance use disorders commonly have high rates of attrition from both treatment and clinical trials (146-148).

Blinding of patients, therapists and researchers to treatment allocation is another prerequisite of the RCT. However, in studies on complex psychosocial interventions, blinding is impossible, and patients might withdraw from the study if they are allocated to a less preferred treatment, which would pose a threat to the between-group equivalence (134, 149).

Consequently, studies involving patients with co-occurring mental and substance use disorders are challenging. This is mirrored by the fact that patients with comorbidity of substance use disorders are often excluded from clinical trials (137, 150, 151). However, if we are to develop tailored treatment approaches for this group of patients, valid research is vital and evaluation reports on projects based on these methodologies imperative.

3. Aims of the thesis

The overall aims were, firstly, to examine whether patients with comorbidities of mental disorders and substance use disorders were detected in psychiatric outpatient clinics and whether they differed from outpatients without substance use disorders (papers I and II). Secondly, the overall aims were to investigate whether integrated treatment, which has been shown to be effective for inpatients with both severe mental disorders and substance use disorders, is equally effective in outpatients with less severe mental disorders, such as anxiety and depression, and substance use disorders (papers III and IV).

Paper I

In this study, we examined whether common and well-known substance use measures are appropriate in detecting substance use disorders in community mental health centres. Our basic assumption was that the presence of substance use disorders in our sample should be on a level with previous findings from other outpatient populations, and that the reliability of the instruments should be confirmed by congruent findings between them.

Paper II

The aims of this paper were to compare patients in community mental health centres with and without substance use disorders regarding 1) differences in socio-demographic characteristics, 2) levels of morbidity, 3) the prevalence of different diagnostic categories, 4) differences in health services provided and 5) differences in the level of improvement in psychiatric symptoms.

Paper III

The aim of this study was to investigate the effectiveness of integrated treatment in patients with substance use disorders and less severe mental disorders regarding 1) the use of alcohol and other substances, 2) the severity of psychiatric symptoms, and 3) the client's motivation for changing his/her substance use behaviour.

Paper IV

The aims of this methodology paper were, firstly, to discuss the methodological adaptations that may be required in clinical research on complex interventions in non-selected clinical populations; secondly, to describe how such adaptations created new challenges in a randomized clinical trial on integrated treatment. We also discuss how these challenges might be understood and highlight the lessons important for future research in this field.

4. Material and methods

4.1 Design and procedures

Papers I and II

In 2002, a study on the development of community mental health centres was designed for the Norwegian Research Council on behalf of the national health authorities as part of an evaluation of the National Plan for Mental Health (152). A cross-sectional design was used. The data was collected from eight Norwegian community mental health centres, with a total catchment area of about 450,000 inhabitants, which was about 10% of the Norwegian population at the time. The clinics were located in both urban and rural parts of the country to cover a representative sample of the Norwegian population. The data was collected during three separate 4-week periods in 2002, 2005 and 2007, and included information from clinicians, general practitioners, patients and their relatives. This study focused on the assessments performed by the clinicians in 2007. The clinicians comprised of psychiatrists, psychologists, psychiatric nurses, and clinical social workers. The clinicians were asked to complete standardized forms for all inpatients and outpatients seen within a specific 4-week period. The forms covered socio-demographic and clinical information.

Papers III and IV

This study was designed to investigate the effectiveness of integrated treatment among patients with anxiety and/or depression co-occurring with substance use disorders in psychiatric outpatient clinics of community mental health centres in Norway. The control condition was treatment as usual. Three to five therapists at each clinic in the intervention group received training in integrated treatment. The clinicians in the control group were promised teaching of the experimental intervention when the study was over.

To obtain external validity, we used a pragmatic RCT design. In order to acquire the calculated sample size, we included multiple centres in the study. Nine centres were included. They were located in the southern, eastern, and central Norwegian Regional Health Trusts. As contamination of knowledge between therapists and patients between groups was an obvious risk, the randomization was at centre level. The centres were randomized by draw and stratified with respect to urban or rural catchment areas. Five centres were drawn to the intervention group and four centres to the control group. Blinding was judged to be impossible, so the allocation to treatment condition was

open at inclusion. In order to secure inclusion, treatment fidelity, protocol adherence, and data quality, we trained and paid one therapist at each centre in a 10% position as a local trial administrator.

All new referrals to the psychiatric outpatient clinics of the centres during the inclusion period were to be screened by the therapists appointed to the patients. New referrals could include patients with a previous treatment history at the centre. Those who scored above the cut-off levels of the screening instruments associated with abuse or dependence were subsequently referred to the local trial administrator to assess eligibility. Patients who fulfilled the inclusion criteria (without fulfilling any exclusion criteria) and consented to participate in the study were included. The patients who were included were assessed by the local trial administrators at baseline and 6 and 12 months of follow-up.

Sample size

As there were no published effect sizes available from studies comparing the effects of integrated treatment with treatment as usual at the time of we planned the study, we computed a within-group effect size based on changes from baseline to follow-up in the absence of a control group in a previous treatment study (153). The effect size in this study was modest (0.57), but with a 5% alpha level and 80% power, the minimum number to treat was 78 patients. With 90% power the number was 108 patients. As we expected between 20 and 30 percent dropout for this group of patients from treatment and assessments, we planned to include a total of 150 patients in the study (i.e. N = 75 in each group). Thus, each of the nine centres was expected to include between 15 and 20 patients.

4.2 Material

Papers I and II:

A total of 2154 patients were included in the study which is about half of all patients reported to the Norwegian Patient Register (NPR) from the eight community mental health centres in a similar period 2 months later (154). Data from the NPR gives a rough estimate of eligible patients as they present the number of patients registered at each clinic during the registration period and not the number of patients actually turning up for their appointment. The number of participants from each clinic varied

from 42 to 409 (median 278), with corresponding participation rates varying from 20% to 83% according to the NPR. There was no information available on eligible patients not included in the study.

Papers III and IV

The inclusion criteria of our study were: new referrals, above 18 years of age, anxiety disorder, and/or depression with or without a personality disorder together with a disorder of abuse or dependence on drugs or alcohol. The exclusion criteria were: psychotic disorder (except episodic drug-induced psychosis), planning to move away from the catchment area during the 12 months duration of the trial, not able to speak or read Norwegian, disorder of abuse/dependence of benzodiazepines or nicotine as the only substance use disorder, and acute illness that required immediate treatment. Those who had an acute illness could be included in the trial after receiving treatment for that illness if they were referred back to the outpatient clinic for regular treatment during the inclusion period. Participants were included if they consented to participation and completed the baseline assessments. The initial inclusion period was from March to December 2007. Because of low inclusion rates, the inclusion period was extended until December 2008. A total of 76 patients (intervention group: 55, control group: 21) were included in the study.

4.3 Research instruments

Papers I and II

Demographic, administrative, and clinical information in addition to one primary and two secondary ICD-10 diagnoses (2) were recorded for each patient (152). The diagnoses were based on routine clinical assessments. No structured clinical interview was used to confirm diagnoses. The Health of the Nation Outcome Scales (HoNOS) (155, 156) were used to measure severity of psychosocial problems in 12 problem areas. The scale ranges from “no problem” (score 0) to “severe problem” (score 4). The alcohol and drug use were rated using the Alcohol Use Scale (AUS) (157, 158) and the Drug Use Scale (DUS) (158, 159), respectively. These scales range from “abstinence” (score 1) to “addiction with hospitalization” (score 5). Drug and alcohol use were measured in four ways: 1) on the basis of the first, second or third diagnoses (ICD-10 F10 – 19), 2) on the response to the HoNOS item three (HoNOS 3), 3) the AUS, and 4) the DUS.

Before the first two surveys in 2002 and 2005, the clinicians at the eight community mental health centres were trained in using the HoNOS, the AUS, and the DUS. Before each of the three surveys they had an optional practice on case vignettes. In 2002, intra-class correlation coefficients (ICC) for the HoNOS were calculated and ranged from 0.60 to 0.89 for the subscales (T. Ruud, personal communication). These coefficients were considered acceptable (160, 161).

Substance use measures

In paper I, we established a combined measure of the different ways of assessing the use of alcohol and drugs to be able to cover all patients in the material with a problematic use of substances and to estimate the prevalence of substance use disorders in this material. The *substance use disorder group* was defined as having fulfilled one or more of the following criteria: 1) a diagnosis of substance related disorder, ICD-10 F10– 19 (first, second or third diagnosis); 2) a high degree of alcohol or drug use (HoNOS 3, scores 2 – 4); 3) a high degree of alcohol use (AUS, scores 3 – 5); or 4) a high degree of drug use (DUS, scores 3 – 5). The *No substance use disorder group* was defined by not fulfilling any of the above criteria.

In paper II, we used the combined measure mentioned above as a grouping variable to investigate whether the patients with substance use disorders differed from the patients with no substance use disorders in regard to socio-demographic variables, the level of morbidity, the prevalence of diagnostic categories, the health services provided and the level of improvement from psychiatric symptoms.

Socio-demographic variables

The socio-demographic variables consisted of age, gender, paid work, in a relationship, living alone and ethnicity.

Variables regarding the level of morbidity

The variables used to investigate the patients' level of morbidity were the HoNOS, except the substance use item as this was used as one of the *substance use disorder group* defining criteria. We categorized the HoNOS scores into two groups: 1) no clinically relevant problem (scores 0-1) and 2) clinically relevant problem (scores 2-4).

Variables regarding the prevalence of different diagnostic categories

The ICD-10 diagnoses were grouped into psychotic disorders (F20-29), mood disorders (F30-39), anxiety disorders (F40-49), personality disorders (F60-69) and other psychiatric disorders (F50-59, F70-99)

Variables regarding the health services provided

The variables used to investigate the health services provided were 1) *psychiatric healthcare received during the last 12 months* and 2) *additional questions about the services in total* (152). The original 6 items of the first variable were categorized into 3 groups; "outpatient or day service at the community mental health centre", "inpatient service at the community mental health centre or hospital" and "outpatient or inpatient addiction treatment". The original three scoring categories of these items were dichotomized into two categories (not received/received). The items of the latter variable were "is the patient being treated at the right level of competence", "are the services sufficiently comprehensive", "are the most important needs of the patient met", "are several services cooperating in making an "Individual Plan" for the patient", and "is the patient also being treated in a psychiatric hospital". These variables were scored "yes/no". An "Individual Plan" means a tailored, comprehensive treatment plan that all patients with a chronic disease are entitled to have according to Norwegian law.

Variables regarding the level of improvement from psychiatric symptoms

The variables regarding the level of improvement were scored on a 7-point scale (152). The items of this scale were grouped into two groups: 1) worse / no change and 2) better. The scoring was based on the clinicians' subjective evaluation of the patients' improvement on the day of the survey, regardless of their length of treatment.

Papers III and IV:

The screening instruments used were the Alcohol Use Disorder Identification Test (AUDIT) (162) and the Drug Use Disorder Identification Test (DUDIT) (163). The cut offs for the AUDIT were set to 6 for women and 8 for men (164). The cut offs for the DUDIT were set to 2 for women and 6 for men (163).

For included patients, the measurements with the AUDIT and the DUDIT were repeated at 6 and 12 months of follow-up. To be able to measure change in substance use during the 12 months of follow-up, the instructions for the AUDIT and the DUDIT were altered to cover substance use during the last 6 months instead of the original "last 12 months".

The diagnostic inclusion criteria were assessed with the Structured Clinical Interview for the DSM-IV diagnoses, i.e. the SCID I (165) and the SCID II (166). Further, the European Addiction Severity Index (EuropASI), chapter E (167-169), the Symptom Check List 90 (SCL-90R) (170-172), and the Substance Abuse Treatment Scale (SATS-r) (173) were used for assessments at baseline, and 6 and 12 months of follow-up.

Outcome measures

The change in the use of substances (alcohol and illegal drugs) during the last six months was examined with the AUDIT and the DUDIT. The change in the use of substances during the last 30 days was investigated with the EuropASI. The EuropASI items regarding substance use were coded into two main variables: *ASI-Alcohol* (i.e. the number of days using alcohol during the last 30 days) and *ASI-Illegal substances* (i.e. the number of days using any illegal substances during the last 30 days). To examine the change in psychiatric symptoms with regard to anxiety and depression, we used the sum scores of the SCL-90R anxiety, depression, and general severity indexes. To examine whether the patient's motivation for changing substance use behaviours changed during the trial, we used the SATS-r. The outcome measures were examined on the individual level.

The local trial administrators had 3 days of training in how to run the project and in using the evaluation instruments including the SCID and the Addiction Severity Index (EuropASI), chapter E. The training on the research instruments consisted of lectures, clinical examples and practising on case vignettes. Their scoring of case-vignettes with the EuropASI, chapter E, was evaluated by a certified teacher.

The validity and reliability of the research instruments used in both studies are discussed in chapter 6.

4.4 Interventions

Papers III and IV

The patients in the intervention group received integrated treatment for both their psychiatric disorder and their substance use disorder. The integrated treatment consisted of the treatment modalities cognitive behavioural therapy and motivational interviewing. In addition, the therapists were to involve the patient's family and have a more active attitude towards the patient in regard to getting the patient into treatment and continuing treatment, for example, by calling or visiting the patient on "no show". The services should also be comprehensive, i.e. directed at a broad array of areas of functioning that are frequently impaired in clients with co-occurring mental and substance use disorders such as housing, vocational functioning, ability to manage the psychiatric illness and family and social relationships (5). The treatment was not manualized although a descriptive treatment guide was provided.

In the control group, the patients received treatment as usual. Treatment as usual is a difficult term to define as it depends greatly on the preference, skills, knowledge, and resources of the therapists delivering it (138). Commonly, the treatment methods used in community mental health centres include psychodynamic and cognitive therapies used with an eclectic approach tailored to meet the needs of the individual patient. However, traditionally the treatments given at psychiatric outpatient clinics have focused on the psychiatric disorders, and given little attention to the substance use disorder.

In both groups the therapists were expected to provide evidence-based treatment for the psychiatric disorder of the patient, including psychopharmacological treatment. The use of such medications was therefore not a focus of the study.

The specific background and work experience of the therapists in this study was not recorded. Generally, the therapists at community mental health centres come from different backgrounds; psychologists and medical doctors in addition to nurses and social workers specialising in psychotherapy. In the intervention group, three to five therapists at each centre and their local trial administrators received training in integrated treatment. This consisted of 35 hours of training in motivational interviewing, cognitive behavioural therapy, involving families, and advice on pharmacological treatment. The training was repeated after 6 and 12 months. The local trial administrators and therapists were encouraged to have regular peer-group meetings at their centre.

The investigators had regular contact with the local trial administrators by phone, e-mails, and visits to the centres.

4.5 Statistical analyses

Paper I

We examined the agreement between the different substance use measures by cross-tabulation. The scores of the AUS and the DUS were combined for the analyses.

To examine whether the merged data differed substantially from the data from each clinic, we repeated the analyses for each clinic separately. To examine whether the results differed between 2007 and 2002 when the clinicians had had extensive training in the use of the instruments prior to the study, we repeated the analyses for the 2002 data for comparison.

Paper II

When comparing two groups the Student's t-test was used for continuous variables and the Pearson's chi-square test was used for categorical variables. The AUS and the DUS were combined for the analyses.

We performed logistic regression analyses to select the adjustment variables. An α-level of 0.05 was chosen when deciding which adjustment variables to include. We included the following variables for the adjusted analyses; *age, gender, in relationship*, *overactive, aggressive, disruptive or agitated behaviour (HoNOS item 1), non-accidental self-injury (HoNOS item 2)* and *problems with activities of daily living (HoNOS item 10)*. We also adjusted for the interaction between *age* and *problems with activities of daily living*. To avoid Type I statistical error due to the number of tests we did Bonferroni correction of the α-level for the main analyses. To adjust for nesting within the centres in the adjusted analyses we performed Generalized Estimating Equations analyses (GEE) with exchangeable working correlation and robust variance estimation. These only gave minor changes in the results compared to the regression analyses. The analyses were performed using SPSS version 18.0 (174).

Paper III

When comparing the background variables of the two groups the Student's t-test was used for normally distributed continuous variables and the Mann-Whitney-U test was used for skewed continuous variables. The Pearson's chi-square test was used for categorical variables. In cases where one or more cells had an expected count less than five, the Fisher's Exact test was used.

To examine whether there were differences between the two groups with regard to treatment response, we used a linear multilevel model where the different response variables were modelled as a function of group and time and adjusted for covariates. The clustering in the data was taken care of by a random intercept at patient level and at centre level. The primary target of analysis was the interaction between group and time, as this indicates the different treatment responses between groups during the course of the trial. We ran both intention to treat and completers analyses.

The intention to treat analyses were adjusted for *age* and *gender* in addition to the following variables: *living alone, having his/her own apartment* and *having compulsory school only,* as these variables showed a statistically significant difference or at least a 10 per cent point difference between groups at baseline. We continued with completers analyses in the same way and adjusted these for *age* and *gender* in addition to the following variables: *being in a relationship, having his/her own apartment, having paid work* and *having compulsory school only or senior high school* as these variables showed a statistically significant difference or at least a 10 per cent point difference between the completer groups at baseline. Completers were defined as having received at least five sessions and having met for at least one follow-up interview.

The residuals were normally distributed for all response variables except for the DUDIT and the ASI variable for illegal substances. The analyses were performed using SPSS version 20.0 (175)

4.6 Ethical aspects

Papers I and II

The study was approved by the Norwegian Data Inspectorate and the Norwegian Regional Ethics Committee. As this study was a cross-sectional study and did not depend on the time and efforts contributed by the patients, the study was not ethically problematic to conduct. On the other hand,

the therapists needed to spend some extra time and effort to complete the assessment forms needed in the study. However, the content of these forms was clinically relevant and not too time-consuming, so the cost-effectiveness of the study procedures should be justifiable.

Papers III and IV

There was a complete discussion of the study with potential participants and written informed consent was obtained after this discussion. The study was approved and monitored by the Regional Committee for Medical and Health Research Ethics in Norway (REC-East). This approval is in accordance with the Declaration of Helsinki.

Clinical trials, commonly, encounter problems in recruitment, follow-up, and adherence, which may reduce power and the probability of demonstrating an effect (type 2 statistical error). This is ethically problematic because one risks wasting financial and human resources. The Medical Ethics Committees therefore assess how realistic each project plan is prior to approval. When researchers encounter such challenges during the course of the trial they are faced with the choice of aborting the study or reinforcing the measures. To be able to make these choices at the appropriate time, researchers need to create strategies on how to handle such difficulties in advance and need to monitor the project continuously. We chose to reinforce the measures by training additional therapists, extending the inclusion period and providing monetary incentives. The latter two reinforcement strategies necessitated additional approval from the Regional Ethics Committee. In either case, whether the researchers choose to abort the study or to reinforce the measures, the researchers have an ethical obligation to report these challenges in a way that prevents other researchers from encountering the same problems.

5. Results

5.1 Identifying co-occurring substance use disorders in community mental health centres. Tailored approaches are needed. (Paper I)

The four instruments that were used to measure the prevalence of substance use in this material all revealed frequencies of substance use disorders on a level with that expected from the general population when used separately and a prevalence closer to that expected in a patient population when combined.

Furthermore, the observed agreement between the four measures was low. About 40 % of the patients who were given a diagnosis of substance use disorders, had a low score on the AUS and/or the DUS, and almost half of those who gained a high score on the AUS/DUS were not given a diagnosis of substance use disorder. Similarly, about 40 % of the patients given a substance use disorder diagnosis achieved a low score on the HoNOS 3, and almost half of those with a high score on the HoNOS 3, were not given a diagnosis of substance use disorder. Additionally, one in five had a high score on the AUS/DUS but a low score on the HoNOS 3, and almost one in four had a high score on the HoNOS 3 and a low score on the AUS/DUS.

All the analyses were repeated on the 2002 data with similar results.

5.2 A cross-sectional study of patients with and without substance use disorders in community mental health centres. (Paper II)

The mean age of the patients was 39 years with no statistically significant difference between the two groups. The patients in the substance use disorders group were more often male, less often in a relationship and more often living alone compared to the 'no substance use disorder' group. Even though these differences were statistically significant, the effect sizes were quite small (176).

We examined if the severity of morbidity as measured by the HoNOS predicted being a substance use disorder patient. We found that the substance use disorders group had significantly more problems with "overactive, aggressive, disruptive or agitated behaviour", "non-accidental self-injury",

"problems with relationships", "problems with activities of daily living" and "problems with occupation and activities".

Regarding comorbidity, 73 % of the patients in the substance use disorder group received diagnoses of somatic or psychiatric disorders in addition to substance use disorders. However, having a mood disorder or having an anxiety disorder was more common amongst the patients in the 'no substance use disorder' group.

We examined if receiving certain health services predicted being a substance use disorder patient. We found that receiving outpatient or day service at the community mental health centres was less common amongst the substance use disorder patients. Receiving outpatient or inpatient addiction treatment was, not surprisingly, more common among the substance use disorders patients. In addition, these patients more often received treatment at too low a competence level according to the therapists.

We examined if the degree of recovery predicted being a substance use disorder patient. We found that having no change or getting worse in regard to "psychological problems" was more common among substance use disorder patients. Having "psychiatric problems", "problems with social functioning", and "problems with practical functioning" was also more common amongst substance use disorder patients, but changed to a borderline significant level after adjustment.

5.3 The effectiveness of integrated treatment in patients with substance use disorders co-occurring with anxiety and/or depression – a group randomized trial. (Paper III)

Baseline demographics

There was a statistically significant difference in age between the groups; otherwise, there were no differences between the groups at baseline. About half the patients were male and had paid work. The majority of patients were not in a relationship, were living with someone, and had completed compulsory education or senior high school only. Regarding their diagnoses, the majority of patients

had an alcohol use disorder and about half the patients had a personality disorder in addition to their mood and/or anxiety disorder.

Looking at the baseline demographics and clinical characteristics amongst the completers, there was a statistically significant difference between groups in regard to *other mental illness* (intervention group: 1/39, control group: 4/17).

Comparing completers to non-completers, we found that there were no differences between them with regard to the amount of substances used or the severity of psychiatric symptoms at intake as measured by the outcome measures at baseline. Nor was there any significant difference in the number of completers between groups.

Summary of the results

Regarding the intention to treat analyses, both groups reduced their use of alcohol and illegal substances during the 12-month course of the trial, as measured with the AUDIT, the DUDIT, and the EuropASI, but the intervention group did not improve significantly more than the control group.

There were no statistically significant changes from baseline in psychiatric symptoms as measured by the SCL-90r, during the course of the trial in either group.

The intervention group had a greater increase in motivation for substance abuse treatment during the 12-month course of the trial than the control group.

The completer analyses showed similar results as the intention to treat analyses on all parameters.

Adverse events

There were no adverse events related to this project. However, one patient included in the intervention group was assessed as having a severe substance use disorder and was therefore referred to a private addiction treatment centre after receiving 3 sessions at the community mental health centre. He died about 8 months later of an overdose at the private addiction treatment centre between the 6 and 12-month follow-up interviews. He was included in the intention to treat analyses and regarded as missing at 12 months.

5.4 When research meets reality: lessons learned from a pragmatic multisite group-randomized clinical trial on psychosocial interventions in the psychiatric and addiction field. (Paper IV)

Flow of centres and participants and protocol deviations

Thirty-five community mental health centres from 3 out of 5 Regional Health Trusts were invited and 10 centres agreed to participate in the study. One of these centres withdrew just before randomization, leaving us with a total of nine centres. Two months into the project, one of the centres in the control group resigned. Another centre in the control group did not manage to include any patients during the time span of the trial, leaving five centres in the intervention group and two centres in the control group.

Thirty-five per cent of the new referrals were screened. Eighteen per cent of the screened patients scored above the cut-off level of the screening instruments, and 31 % of these patients were referred to the local trial administrator for the baseline evaluation. Seventy-six patients, 55 in the intervention group and 21 in the control group were enrolled.

The recruiting period was initially from April until December 2007 but was extended until December 2008. The follow-up period continued one year after inclusion. After inclusion, 16 patients in the intervention group and 4 patients in the control group received fewer than 5 sessions and/or never returned for follow-up interviews. This left 56 completers (control group: 17, intervention group: 39).

6. Discussion of the methodology

According to Shadish, Cook, and Campbell, the term validity refers to the approximate truth of an inference (136) (p. 34). In 1957, Campbell was the first to define two types of validity; internal and external (136, 177). Cook and Campbell elaborated this typology into four related categories; statistical conclusion validity, internal validity, construct validity and external validity (178). Following their lead, Shadish et. al. define these categories as follows.

Statistical conclusion validity refers to the appropriate use of statistics to infer whether the presumed independent and dependent variables covary (type 1 statistical error) and how strongly they covary (type 2 statistical error) and, thus, also considers the role of effect sizes in experiments (136).

Depending on the former, *internal validity*, also called *local molar causal validity* (179), refers to inferences about whether the observed co-variation between A and B reflects a causal relationship from A to B. This presupposes that A precedes B in time, that A co-varies with B (i.e. statistical conclusion validity), and that no other explanations for the relationship are plausible (136).

Construct validity refers to making inferences from the sampling particulars of a study (i.e. the observed persons, settings, cause and effect operations) to the higher order constructs they represent. It represents a twin problem; understanding constructs and assessing them. The naming of things, i.e. making constructs, is a key problem in all science, for names reflect category memberships that themselves have implications about relationships to other concepts, theories, and uses (social, political, economic, etc.) (136). Many studies use structured interviews, questionnaires and assessment forms that have been translated from one language (primarily English) to another. In addition to a linguistic translation, such research instruments need to be cross-culturally adapted to reflect what they are supposed to measure (180).

External validity is about whether inferences from the causal relationship hold over variations in persons (units), settings, treatment variables, and measurement variables. Both construct and external validity refer to generalizations. The former refers to generalizations from operations to constructs and the latter refers to generalizations from samples of persons, settings, and times achieved in a study to and across other relevant populations (136).

In the following sections, I will discuss possible threats to each type of validity in our studies, how we might have overcome them, and how these threats might affect the conclusions that can be drawn from our studies. Our first study (papers I and II) has a cross-sectional design and cannot infer causal relationships, thus, the question of internal validity will not apply.

6.1 Discussion of the methodology of study 1 (papers I and II)

6.1.1 Statistical conclusion validity

Proper use of statistical tests

All the continuous variables had normal distribution, which justifies the use of the Student's t-test. As the outcome variable was dichotomous, we performed logistic regression analyses to investigate the relationship between the outcome and explanatory variables (paper II). As we included patients from different centres, one might expect nesting within each centre which could result in over- or underestimating effect sizes. To adjust for nesting, we performed Generalized Estimation Equation analyses (paper II).

Fishing related problems

This study was part of an evaluation of the National Plan for Mental Health and adapted to our study aims. As we conducted a large number of tests there is a probability of artificially inflating statistical significance. To minimize this problem, we only tested variables that were in accordance with the pre-test hypotheses that we wanted to investigate. In addition, we did Bonferroni correction of the α-level to avoid Type I statistical error (181). Further, we added confidence intervals to the effect sizes as this gives more information about the actual size of the effects. For the same reason, we reported exact p-values instead of describing the results dichotomously; i.e. as significant or non-significant.

Reliability of measures

Reliability of measures concerns issues like the number of measurements (more items or more raters) and the quality of measurements (better items and better training of raters, i.e. inter-rater reliability). If either variable is measured unreliably, a conclusion about co-variation may be inaccurate (136).

In our study, the prevalence of substance use disorders was measured by a composite adapted approach based on the AUS, the DUS, the HoNOS, and the ICD-10 diagnoses.

The AUS and the DUS have proved strong inter-rater reliability (158). We did not assess the inter-rater reliability amongst raters in our study. However, the instruments consist of straightforward lists of criteria that correspond to the DSM, and, hence, should be easy to interpret consistently between raters. On the other hand, the reliability of the instruments relies on how well the clinicians know their patients and use all available information related to the issue (158). The clinicians were instructed to do so, and we have no information they did otherwise.

The HoNOS have also proved good inter-rater reliability (155). The inter-rater reliability of the Norwegian translation used in our study was assessed prior to the survey in 2002 and ranged between acceptable and good between subscales (ICC ranging from 0.60 – 0.89) (160, 161).

We did not assess the inter-rater reliability prior to our survey in 2007. However, we found no significant differences when we compared the results from 2007 with the results from 2002 with regard to the prevalence of substance use disorders obtained with the AUS, the DUS, and the HoNOS.

We had a large number of raters (and patients), so, if there were errors in the scoring of these variables, given that these errors were random, one would expect the impact of these errors to be small (i.e. random error of measurements).

Restriction of range

We chose to dichotomize several of our continuous outcome variables, which would restrict the range and lower power. However, we found it important to do so to ensure that the differences we might find would be clinically relevant. Otherwise, because of the large sample size, we would get statistically significant differences on the outcome measures between groups that were not relevant from a clinical point of view.

6.1.2 Construct validity

Inadequate explication of constructs

The AUS and the DUS are five point scales based on the DSM-III assessing the severity of substance use disorders. The clinicians are supposed to use all available data (patient journals, collateral information, patient interview, and so forth) to establish the ratings. These instruments obtained good validity when compared to consensus-based diagnoses of substance use disorders (157, 158, 182). In our study, we used Norwegian versions of these instruments, translated for the purpose of the TIPS-project (Early Identification and Treatment of Schizophrenia) (183) by psychiatrist E. P. Ellefsen. The Norwegian translation was translated back to English by a project co-worker and the result discussed within the research group who approved the translation (personal communication from the project leader at the time, Professor I. Melle). The reliability and the validity of the Norwegian translations have not been assessed.

The HoNOS consist of 12 items covering broad psychosocial areas. This instrument has proved good validity compared to longer and well-established instruments (155). We used a Norwegian version of the HoNOS, which was translated by psychiatrist T. Ruud and approved by the Royal College of Psychiatrists Research Unit in London. The reliability and the validity of the Norwegian translation have not been assessed.

The diagnoses were set by the clinicians according to the ICD-10. No structured diagnostic interviews were used to assess diagnoses. This mirrors the reality in everyday clinical settings where structured diagnostic interviews are not commonly used (184). Poor agreement between diagnoses based on clinical assessments and those based on structured clinical interviews has been shown in several studies (185-188). In addition, our clinicians had different professional backgrounds and experience, so the validity of the diagnoses set could be questioned. This is why we only used main diagnostic categories when we analysed the data. Several studies have shown that substance use disorders are often missed in clinical settings without a structured clinical interview (63, 189). The findings of our first paper confirm this as we found several discrepancies between the prevalence of substance use disorders when assessed using the different measures (the AUS/DUS, the HoNOS item 3, and the ICD-10 F10-19).

To investigate the health care received, we used assessment forms that were made by the research group. These questions were simple lists of what health care the patient had or had not received, so

there was no need to assess psychometric properties of these variables. The words used in the variables corresponded to the actual nomenclature used (e.g. inpatient, outpatient, individual plan etc.), so the validity of the constructs should be good. Further, the validity relies on the extent to which the clinician has been thorough in finding the information to put into the form.

To assess the level of improvement in psychosocial symptoms we also used assessment forms made by the research group. The scoring was based on the clinicians' subjective evaluation of the patients' improvement on the day of the survey, regardless of length of treatment. Psychometric properties or other means of construct validity were not assessed. Item 1 in this questionnaire is called “level of improvement since the day of intake from psychiatric symptoms” and item 2 is called “level of improvement since the day of intake from psychological symptoms”. One might ask what the difference is between these two questions, which received approximately the same scores.

Construct confounding and mono-operation bias

In an experiment the operations are rarely pure representations of constructs (136), which means that the researcher’s definition of, for example, a grouping variable might be incorrect (i.e. construct confounding). Many experiments use only one operationalization of each construct, which might underrepresent constructs, contain irrelevancies and lower construct validity (i.e. mono-operation bias) (136).

In our study we wanted to compare patients, with and without substance use disorders, who were treated at community mental health centres. We found that no single operation / instrument could define these groups, so we used a combined measure of AUS/DUS, HoNOS item 3 and the ICD-10 diagnoses F10-19. In this way we believe that we managed to include most of the patients of interest.

6.1.3 External validity

Interactions of the causal relationship with units and settings

External validity addresses whether the results from a study will be valid in another population and setting (e.g. rural or urban) than the one that was studied. In our study, we intended to include all patients (i.e. units) at the involved centres during a specific four-week period. The centres (i.e. settings) were chosen to represent both urban and rural parts of Norway and their total catchment area included about 10% of the Norwegian population at the time. These inclusion criteria were chosen to include a representative sample of patients at Norwegian community mental health centres, and, so the results should be valid for all patients at different community mental health centres in Norway. However, the total number of patients included in the study was only about half the eligible patients, varying between 20% and 83% between centres. There was no information available about the patients not included in the study. If the patients included in the study were selected in a systematically different way from those not included, it would bias our results. An example could be if the therapists only included patients with fewer or more "straight forward" problems, so as to lessen the work of completing the assessment forms. However, if patients were included randomly, it would not bias our results. An example of such a scenario would be if the therapists included patients whenever they were reminded or remembered to include patients for the study. We have no way of knowing how the selection was performed, so we do not know if our results are valid for patients and centres other than those that were studied.

6.1.4 Limitations of the designs

Our first study has a cross-sectional design. This type of design is suitable for studying prevalence, associations, and risks, but as all data are collected at the same point in time, they cannot infer causation (190, 191). As we have only used this data to calculate prevalence and associations, these premises are not violated.

6.2 Discussion of the methodology of study 2 (papers III and IV)

6.2.1 Statistical conclusion validity

Proper use of statistical tests

When comparing the background variables of the two groups the Student's t-test was used for normally distributed continuous variables and the Mann-Whitney-U test was used for skewed continuous variables. The Pearson's chi-square test was used for categorical variables. In cases where one or more cells had an expected count less than five, the Fisher's Exact test was used. The residuals were normally distributed for all response variables except for the DUDIT and the ASI variable for illegal substances. As the changes between groups regarding these outcome measures were not statistically significant, we did not perform additional analyses to account for this skewness. As we included patients from different centres, there is a risk of nesting within each centre which might result in an over- or underestimating of effect sizes. To adjust for nesting, we performed Generalized Linear Modelling analyses.

Low statistical power

In our study, a low inclusion rate together with high attrition led to low power, thereby making the study vulnerable to type 2 statistical error. We did many tests, all according to our pre-test hypotheses. Nevertheless, we chose not to do Bonferroni correction, as this would increase the risk of type 2 statistical error even further. Instead, we kept the α-level at the standard 5% level.

Reliability of measures

The SCID 1 and the SCID 2 are well-known structured clinical interviews that have proved strong inter-rater reliability (192). The inter-rater reliability of the Norwegian version of the SCID 1 has also proved to be high (193). In our study, the local trial administrators were taught how to use the SCID 1 and 2 by two experienced psychologists certified in the use of these interviews. The local trial administrators practised on case vignettes that were assessed by these two teachers. No inter-rater reliability tests were performed. This was a pragmatic choice, balancing the cost and the purpose of the use of these instruments as they were not going to be used as outcome measures or for sub-diagnostic purposes. We believe they served their purpose in this way.

Regarding the EuropASI, we only used the part of the instrument that assesses the patient's previous and current drug use (chapter E). The local administrators at the centres were taught how to use this part of the instrument by a certified teacher. We did not perform inter-rater reliability tests, which might prove a problem to reliability of measures. The raters scored on case vignettes that were evaluated and approved by the teacher.

Regarding the SATS-r, the local trial administrators were taught how to use the instrument by experienced researchers in the research group. The SATS-r has proved strong inter-rater reliability (173). We did not perform inter-rater reliability tests among our raters; however, according to the developer of the SATS-r, clinicians are capable of using the instrument consistently and meaningfully with moderate training and reasonable familiarity with their clients (173). Thus, we have reason to believe that the instrument is a reliable measure also in the context of our study.

Restriction of range

Variables might be restricted to a narrow range if an experiment compares two highly similar treatments, e.g. comparing an experimental intervention to standard treatment. As the standard treatment is also effective, the difference between the two will be small and the range narrow. This restriction lowers power and attenuates bivariate relations (136). The restriction can be decreased by comparing treatment to no-treatment.

Our study is an effectiveness study, i.e. investigating the effects of our intervention under "real-world" circumstances, so comparing our experimental treatment to no-treatment was not an option. We, therefore, compared our experimental treatment to the standard "treatment as usual", thereby narrowing the range and lowering power. Another aspect of this is that there is no good definition of the term "treatment as usual", i.e. the control condition. There could have been therapists in the control group who were providing elements of the experimental treatment. This would further narrow the range and lower power.

Reliability of treatment implementation

If treatment is implemented inconsistently from site to site or from person to person within sites, conclusions about co-variation will be affected and decrease effect size. On the other hand, variable implementation may reflect tailoring of the intervention to the recipient in order to increase its effects (136).

In our study, we wanted to investigate our intervention under “real-world” conditions. In everyday clinical practice, clinicians face a wide range of disorders and this requires an eclectic approach, tailored to meet the needs of the individual patient. For this reason, our treatment was not manualized, but a descriptive clinical guideline manual was provided and used in staff training, which could threaten the reliability of treatment implementation.

Another threat to the reliability of implementation is whether the trained therapists actually used the intervention they were taught, or if they continued to provide the therapeutic techniques that they already knew well, i.e. treatment as usual. This would further restrict the range between the two conditions and reduce power. We did not perform treatment fidelity tests to investigate this matter.

Extraneous variance in the experimental setting

If features of an experimental setting artificially inflate error, conclusions about co-variation can be inaccurate, for instance, administrative changes that distract practitioners (136).

During the planning phase of our project, as part of the Addiction Treatment Reform, new national mental health service guidelines were published. These guidelines were interpreted differently by the different centres. One interpretation was to establish separate addiction outpatient units as part of the community mental health centre. This meant that the psychiatric outpatient clinic of the centre had hardly any patients with comorbid mental and substance use disorders. This could produce an extraneous variance in the experimental setting.

In addition, one of the centre leaders resigned shortly after the project started. His successor had little interest in the project and did not encourage or support the staff to continue the screening procedures required in the study. Unless the importance of screening is strongly emphasized by the local trial administrator and/or the research group and followed by strong support from the clinic management, such new routines are easily forgotten and this might further produce extraneous variance in the experimental setting.

Heterogeneity of units

When participants in a study are heterogeneous within conditions on an outcome variable, this heterogeneity will obscure systematic co-variation between treatment and outcome and give wide standard deviations. A solution would be to apply strict inclusion criteria. This, however, would reduce external validity (136).

Most of the patients in our target group are excluded from clinical research because of high attrition rates. This results in lack of knowledge about effective treatments in this group of patients. For this reason, we wanted our study sample to reflect the heterogeneous group of patients seen in everyday clinical practice. We therefore applied broad inclusion and narrow exclusion criteria, which would secure good external validity at the cost of internal validity, reducing effect-size and power.

6.2.2 Internal validity

Ambiguous temporal precedence

Sometimes it is unclear whether A precedes B or vice versa, and the fact that A occurs before B does not necessarily mean that A causes B (136).

Our study was a longitudinal experimental study, which only allows as potential causes those variables that occurred before their possible effects. However, the study was not conducted in a laboratory, and participants were free to seek additional treatment elsewhere. If this happened, the additional treatment could affect treatment outcome. However, participants of both treatment groups could do this so it should not affect group differences in outcome measures. See also *treatment diffusion*.

Selection

Our study had random assignment to treatment conditions to minimize the risk of baseline differences between groups. However, this random assignment was carried out at centre level, not individual level, so there might still be a risk of selection bias and baseline differences between individuals. On the other hand, in all centres the participants were chosen by the therapists using a series of screening and assessment procedures that were the same in each centre, and possible nesting within centres was accounted for by multilevel statistical analyses.

Further, as this is a group randomized trial consisting of only seven centres, the results could be biased if the performance of one centre was much better or much worse than the others. To handle this potential bias, we have used a random intercept in our linear multilevel model.

History and maturation

In our study, the time schedule for the assessments was originally the same. However, as the inclusion rate was greater in some community mental health centres than in others, one centre had finished including its patients while others continued into the following year. This means that the participants could have experienced different historical events that could have affected outcome measures.

As we wanted to have strong external validity, we chose participants of the same age groups that are normally treated at the community mental health centres, i.e. between 18 and 65 years of age. This means that the participants were heterogeneous regarding age and could have experienced different maturation changes.

Our study is a multi-centre study with centres from both urban and rural areas to include a representative sample of the population. For this reason, the centres were spread over a large geographical area. This could mean that they were susceptible to different historical events and maturation changes. We used multilevel statistical analyses to account for such nesting within groups.

Regression artefacts

When participants are selected for their extreme scores, they will often have less extreme scores on other variables, including retest on the original variable (136). This phenomenon is called “regression to the mean” (194-198). One way of explaining this is that every measure has a true score component, reflecting a true ability, and a random error component that is distributed normally and randomly around the mean of the measure. In psychotherapy this phenomenon is called “spontaneous remission” and is explained by the fact that patients come to therapy when they are more distressed than usual and therefore tend to improve even without therapy (136).

In our study, we included new referrals to the community mental health centres who scored above a certain threshold level on alcohol and drug use together with diagnostic features of substance use

disorders and depression or anxiety. According to the theory of regression to the mean, one could expect these patients to improve on the outcome measures independently of treatment. This could threaten internal validity. However, this phenomenon would be expected to occur in both treatment groups so it would not affect group differences on outcome measures.

Attrition

Loss of respondents to treatment or to measurement can produce artefactual effects if that loss is systematically correlated to treatment conditions. This is a subset of selection bias that is not controlled by random assignment to conditions (136).

In our study, we experienced dropout from both treatment and follow-up assessments. The dropout from treatment (defined as having had fewer than 5 sessions) did not differ between centres, but the dropout from follow-up assessments did. One centre managed to complete follow-up interviews for all patients at 6 and 12 months. At the other extreme, one centre lost 6 out of 14 patients at both follow-up sessions. The other centres lost 1–2 patients each from both follow-up sessions. The centres with the highest and the lowest dropout rates were two of the five centres in the intervention group. Otherwise the dropout rates did not differ between the centres or treatment groups, so we do not expect them to produce artefactual group differences. In addition, the general linear multilevel model that we used for the statistical analyses is meant to account for missing variables.

Testing

Taking a test may influence subsequent scores when the test is taken again. This may be because of acquired practice and familiarity with the tests when repeating them (136).

In our study, we repeated several of the tests at baseline and at 6 and 12 months of follow-up. One possibility is that taking tests about use of alcohol and drugs might motivate participants to reduce their use of substances independently of the treatments received. We therefore conducted the same assessments in both treatment groups so it should not produce group differences on outcome measures.

Instrumentation

This refers to changes in the actual instruments used, for instance, changes over time in the way a measure is taken or changes in the meaning of specific variables over different life stages (136).

Our study was a longitudinal study with repeated testing over a period of two years in total. We do not believe that this time span would affect the meaning of the variables used in the tests. The same local trial administrators conducted the assessments throughout the whole study period. Of course, these local trial administrators may, have become more proficient in conducting and interpreting these tests over time. However, if this were the case, it would have occurred in both treatment groups and should not affect group differences at outcome

6.2.3 Construct validity

Inadequate explication of constructs

The AUDIT is a self-report questionnaire that was developed by the World Health Organization in collaboration with six different countries, Norway among them. It has proved to have strong validity and good sensitivity and specificity in identifying problematic drinking of alcohol at the chosen cut-off levels of 8 for men and 6 for women (162, 164). The instrument was developed to identify hazardous drinking of alcohol at an early stage in primary care (162). Since then, the AUDIT has proved to be applicable over a broad range of samples and settings, including estimates of the prevalence of alcohol problems among patients with somatic and mental illnesses (164). In a review of the literature, Reinert et. al. found a high degree of international consistency regarding reliability and validity (164). The DUDIT was developed by a Swedish research group as an analogous instrument to the AUDIT and has also proved to have strong validity and reliability (163). The DUDIT was translated into Norwegian by Landheim and colleagues at the Norwegian National Advisory Unit on Concurrent Substance Abuse and Mental Health Disorders and approved by the Swedish research group headed by A. H. Berman. Apart from this, the reliability and validity of the Norwegian translation has not been assessed.

In our study, we used these instruments both as an initial screening for hazardous use of substances and as a measure for change in substance use from baseline to 6 and 12 months of follow-up. As our follow-up times consisted of two 6-month periods, we changed the instructions for the AUDIT and the DUDIT to cover substance use during the last 6 months instead of the original 'last 12 months'.

We have no reason to believe that any of these alterations would affect the validity of these instruments. Both instruments have proved to have good test-retest reliability (164, 199). Nonetheless, as the AUDIT and the DUDIT are self-report instruments, the reliability relies on the respondent's ability and willingness to answer truthfully (164, 200). Initial screening scores could have been affected if the patient did not feel safe enough to be honest about his or her substance use before he or she got to know the therapist, or if the patient was in denial at this initial stage of treatment. If this were the case, it would mean that we cannot rely on the initial (baseline) scores. On the other hand, one would expect this to happen in both treatment groups so it should not affect group differences at outcome.

The SCID 1 and the SCID 2 are well-known structured clinical interviews. The validity of the SCID 1 has proved to be strong when conducted by clinical specialists who have been trained in using the instrument (188). The validity of the SCID 2 has proved to be strong regarding diagnoses of disorders with distinctive, behaviourally defined psychopathology (such as antisocial and schizotypal personality disorders), and not so strong validity regarding disorders whose items require more inference on the part of the interviewer (such as narcissistic and self-defeating personality disorder) (201). The SCID 1 and the SCID 2 interviews have been translated to Norwegian by Vogel and colleagues (202) and Friis and colleagues (203), respectively. The translations were discussed in the research group that approved the translation (personal communication with Prof.Emeritus S. Torgersen who was in the research group at the time). These instruments are widely used in clinical and research settings in Norway although studies of the reliability and validity of the Norwegian translations have not been conducted.

The EuropASI is the European version of the well-known Addiction Severity Index (ASI) (169, 204) which has proved to have good reliability and validity (205). The EuropASI has been translated into nine languages (204), including Norwegian. The Norwegian translation was carried out by Hidle, Lauritzen, and Skretting in 1997. It was translated back into English by a professional translator and approved by the developers of the EuropASI (personal communication with G. Lauritzen). The instrument has been used in several studies amongst patients in addiction treatment in Norway (206-209) and has been found useful for clinical and research purposes (210, 211), although studies of the reliability and validity of the Norwegian version have not been conducted.

The SCL-90 (170-172) was developed as a self-report instrument in 1977 and has been widely used in clinical and research settings. In our study, we used a Norwegian version of this instrument

translated by Nilsen and Vassend (212, 213) which has shown comparable reliability and validity with the original instrument (212). The original SCL-90 has proved moderate to good levels of theoretical agreement on nine symptom constructs in a heterogeneous group of psychiatric outpatients (171). However, the psychometric properties with regard to factorial structure have been much debated and several studies have suggested that the instrument is more useful as an indicator of general psychiatric distress as measured with the General Severity Index (GSI) parameter of the SCL-90 (214-217). In our case, this would mean that we can only rely on the GSI scores as an outcome measure in our study. Others have found that anxiety and depression are distinguishable by self-report with the use of the SCL-90 in homogeneous groups of patients with anxiety or depression, respectively (218). This could mean that the use of the sum-scores of anxiety and depression, as we used in our study, are valid as outcome measures as our patients were diagnosed with anxiety and/or depression at inclusion. Others have found that the reliability of the instrument might be questioned because patients might over- or underreport their symptoms depending on what they want to communicate to the therapist (e.g. a cry for help or denial) (219). We have no way of knowing if this is the case in our study, but if it were the case, we would expect it to occur in both treatment groups so it should not affect group differences at outcome

As integrated treatment is motivation-based, i.e. adapted to the patient's motivation for change, an approach that is based on the Stages of Change (91, 92) and the closely related Stages of Treatment (94), we used the SATS-r (158, 173) to assess the patient's motivation for changing his or her substance use behaviour during the trial. The SATS-r has proved to have strong test-retest reliability together with strong construct validity compared to comprehensive consensus evaluations (173). We used a Norwegian version of this instrument. The translation process of this instrument is unknown.

Construct confounding

The operations in an experiment are rarely pure representations of constructs from "the real world" (136), and as soon as we apply inclusion and exclusion criteria to define our target population, we apply restrictions that might or might not include the intended target population.

We intended to include patients with substance use disorders co-occurring with anxiety and/or depression at psychiatric outpatient clinics. We had quite broad inclusion and narrow exclusion criteria to secure external validity. We believe that we managed to include the intended target group in this way.

Mono-operation bias and mono-method bias

Construct validity will be lower in single-operation research because they both underrepresent constructs and may contain irrelevancies (i.e. mono-operation bias). When all operations use the same method (e.g. self-report), then this method becomes part of the construct studied (i.e. mono-method bias) (136).

With regard to our first aim, to evaluate the patients' use of substances, we used two measures; The AUDIT/DUDIT and the EuropASI. The AUDIT and the DUDIT are self-report measures that assess alcohol and illegal drug use behaviour, respectively, during the previous 6 months. The EuropASI, chapter E, is part of a structured interview that measures the quantity and frequency of the use of different substances during the last 30 days and the last 6 months. In this way, we managed to evaluate different aspects and time frames of the patients' substance use.

With regard to our second aim, the severity of psychiatric symptoms (i.e. anxiety and depression), we used one measure; the self-report instrument SCL-90R, specifically the sum-scores of anxiety, depression and the general severity index as outcome measures. The instrument comprises several questions about different aspects of anxiety and depression during the previous six months and, in this way, looks at different aspects of the issues in question.

Regarding our third aim, assessing the patients' motivation for changing his / her substance use behaviour, we used the SATS-r. This is a clinician-rated scale where the clinician is supposed to use all available data to evaluate which phase of changing his or her substance use the patient is in, thus, taking into account different aspects of the issue when assessing the patient.

Confounding constructs with levels of constructs

This concerns which levels of each facet of the construct are actually studied. The results might be different if different levels are studied. For example, in treatment-control comparisons the treatment might be implemented at such low levels, that no effects are observed, leading to the incorrect conclusion that the treatment had no effect. The right conclusion would be that the treatment implemented at such a low level had no effect (136).

In our study, we did not have a good measure for treatment fidelity, which means that we do not know if the treatment was implemented at a sufficient level for the patients in the intervention group to receive a different treatment from those in the control group. Many studies have shown that implementing new procedures is challenging, demanding and costly in time, and in human and monetary resources (220-225). If the experimental intervention was not implemented sufficiently, it could explain the lack of significant differences between the groups with regard to improving the use of substances and psychiatric symptoms. On the other hand, there was a significant group difference in motivation for treatment in the intervention group, which indicates that the intervention was implemented at a sufficient level to detect differential effects in some aspects.

Reactivity to the experimental situation

The responses of the participant not only reflect the treatment received but also the participants' perception of the experimental situation so these perceptions are part of the constructs tested (136). In addition, the fact of being asked about your substance use behaviour might start to induce a process of changing the behaviour.

To address this problem, we used exactly the same procedures for all assessments conducted at the same time points; i.e. at baseline, 6 and 12 months of follow-up, in both treatment groups.

Experimenter expectancies

The participants' responses can be influenced by the expectations of the experimenter about desirable responses. These expectations will then be part of the treatment construct tested (136).

The initial screening with the AUDIT and the DUDIT was performed by the different therapists at the community mental health centres. If the therapist expected the patient not to have a problematic use of substances, this expectation might affect the patient's score. This would result in a lower prevalence of problematic substance use amongst patients, and ultimately, a lower inclusion rate in the study. As recruitment to the study was slow in many of the community mental health centres, and not happening at all in one of the centres, this is an aspect that has to be considered.

All assessments were conducted by the local trial administrators and not by the person actually treating the patient. However, there were two exceptions. One of the patients became suicidal and wanted to change her therapist or leave treatment. The trial administrator, who was a senior

therapist, had to take action immediately and take on the therapy of that patient. She conducted the 12-month assessment of this patient while she was also her therapist. One of the other patients left treatment when he was committed to prison. When he was referred back to the centre after imprisonment, the trial administrator, by mistake, was assigned as his therapist. She conducted both follow-up assessments while she was also his therapist. We have no reason to believe that the assessments of these two cases would bias the results.

The best way of addressing this type of threat to validity would be blinding of treatment conditions to the therapist, the patient, and the assessor. This is, however, impossible in studies involving psychosocial interventions. It would have been possible to blind the assessor to treatment conditions if all patients were assessed at a neutral place (not at the treatment centre), but this would involve a number of practical difficulties and, most likely, result in even higher attrition from assessments. On the other hand, one would expect the assessors of both treatment conditions to want to show that their intervention gives the best results (see *compensatory rivalry* below), so this should not affect group differences.

Novelty and disruption effects

A novel innovation may result in unusually good responses from the participants if they get excited about this new treatment. On the other hand, the participants might respond unusually poorly to the introduction of repeated new innovations or to an innovation that disrupts their routine. Thus, these responses must be included as part of the treatment construct descriptions (136).

In our study, this issue would depend greatly on how the study was introduced to the patients by the therapists, and, this could affect the inclusion into the study. How the study was introduced to centres and followed up by the local trial administrators (and the research group) could affect the attrition from the study.

Regarding inclusion, one of our centres (control group) did not manage to include one single patient even though the inclusion period was extended by one year. They had the largest percentage of patients under the cut-off scores of the screening instruments, the highest number of patients handing in a blank screening form or not giving oral consent to participate, and they were the only centre where the clinicians deemed a number of patients not eligible for participation. Several explanations are plausible; it could be a disruption effect, or the result of insufficient implementation

of the study, or inadequate support from the clinical administration or the research group. These problems could also be related to *resentful demoralization* discussed below.

Regarding attrition, one centre (in the intervention group) managed to complete all interviews for all participants at 6 and 12 months of follow-up. At the other extreme, one centre (in the control group) lost 6 out of 14 patients at both follow-up sessions. This could be the result of how well the local trial administrators managed to motivate the patients to participate, or how well the research group and clinical management managed to motivate and support the local trial administrators.

Compensatory rivalry

Assigning units to experimental and control conditions may motivate participants not receiving the experimental intervention to show that they can do as well as those receiving the intervention. This compensatory rivalry must then be included in the description of the treatment construct (136).

In our study, the leader of one of the centres in the control group said that they would do what they could to perform just as well as the intervention group. We have not assessed whether the patients of this centre performed better than others in the control group, but this is the only centre in the control group that managed to include the minimum expected amount of patients and that only lost 2 out of 15 patients at both 6 and 12 months of follow-up.

Resentful demoralization

Participants may respond more negatively than otherwise if they do not receive the desirable (experimental) treatment. Thus, this resentful demoralization should be included as part of the description of the treatment construct (136).

We encountered this attitude when we first included centres, as some of the clinic leaders stated that they would not want to participate in the study if they were allocated to the control group. Additionally, one of the included centres withdrew two months after they were allocated to the control group. They stated this was because of workload and staffing problems, but one might speculate if one of the reasons was that being part of the control group was not motivating enough to continue.

Treatment diffusion

When participants receive services from a condition to which they were not assigned, it makes describing the constructs of both conditions more difficult (136).

Contamination of knowledge between therapists and patients between groups was considered an obvious risk, and we therefore randomized at centre level. However, the patients participating in the study, like all other patients, are free to seek services elsewhere. Further, in the control group, it would be unethical not to refer patients to addiction treatment if the centre did not feel they had the necessary competence at their psychiatric outpatient clinic.

We did not systematically register this, but through communications with the local trial administrators, we know that several patients received treatment elsewhere. In the control group, 4 out of 15 patients in one centre were referred to group therapy, and another patient, who was lost to follow-up, received treatment at an addiction outpatient clinic. In the intervention group, one patient continued treatment at an addiction outpatient clinic after receiving 15 sessions at the assigned community mental health centre. At another centre, one patient was referred to inpatient addiction treatment after receiving 5 sessions at the centre. This patient died from an opioid overdose a couple of months later. In addition, one patient at another centre received psychomotoric physiotherapy and never turned up for treatment sessions at the assigned community mental health centre. In total, 5 patients out of 21 in the control group received additional treatment elsewhere, whilst this was only the case for 3 out of 55 in the intervention group. The three patients that were referred to addiction treatment were described as having a severe substance use disorder.

The control condition, called “treatment as usual”, is a difficult term to define as it depends greatly on the preference, skills, knowledge, and resources of the therapists delivering it (138). The fact that some of the patients in the control group also got additional treatment makes the control condition even more difficult to describe and, ultimately, might affect our results by reducing effect sizes.

6.2.4 External validity

Interaction of the causal relationship with units

Interaction of the causal relationship with units concerns whether our results can be generalized to people other than those studied. We intended to secure strong external validity to be able to generalize our results to the average patient at community mental health centres. We accomplished this by having broad inclusion criteria and narrow exclusion criteria. However, only 35% of the eligible patients were actually screened. Of those who scored above the cut-off levels of the screening instruments, only 31% were actually referred to the local trial administrators for baseline evaluation. In the end, only 4% of the total number of screened patients, and 24% of the patients who scored above the cut-off levels of the screening instruments were included in the study.

This brings the external validity of the results into question. We have no way of comparing the patients included with those not included in the study. The question is whether the patients screened and referred for baseline evaluation were selected systematically or randomly. As discussed previously, different reasons for the therapists not to screen or refer patients for evaluation might be poor implementation of the study, an effect of novelty disruption, or an effect of resentful demoralization. In all these cases, one would expect a random selection of patients, which would not affect the representativeness of our sample. On the other hand, the total number of patients included and followed-up throughout the study is quite small (i.e. 76 patients in total, of whom only 56 are defined as completers). Hence, the interpretation of the results and generalization to patients other than those studied must be done with great care.

Interactions of the causal relationship with settings

This concerns whether the causal relationship is valid across different settings. The first challenge we encountered was recruiting community mental health centres. Thirty-five centres from 3 out of 5 Regional Health Trusts were invited but only nine centres agreed to participate. We do not know if the centres that agreed to participate are systematically different from those that declined, e.g. have lower workload, better staffing etc. Given the challenges the participating centres encountered, there is no indication that this was the case. We therefore have no reason to believe that the participating centres differed significantly from other centres.

After allocation to treatment conditions, one centre withdrew from the study and one centre did not manage to include any patients during the timespan of the study. This left us with seven centres. These centres were spread across the middle, western and southeastern parts of Norway, comprising both urban and rural areas. They should be representative of the settings of community mental health services in these parts of the country. Whether they are also representative of settings in other parts of the country, the northern part in particular, can be questioned.

Interaction of the causal relationship over treatment variations

This concerns whether an effect found with one treatment variation might hold with other variations of the treatment, if the treatment is combined with other treatments, or when only parts of the treatment are used (136).

We have investigated if the effectiveness of integrated treatment, which was originally designed for people with co-occurring severe mental disorders and substance use disorders, would apply to other patient populations, e.g. patients with less severe mental disorders co-occurring with substance use disorders. These patients have a higher level of psychosocial functioning, including activities of daily living, and housing etc., than those with severe mental disorders so not all parts of the original treatment would apply at the same degree, e.g. extensive outreach work. Another question is whether the treatment constituents we used are applicable to other patient groups and, if so, to what extent? Yet, another question is whether all the treatment constituents we used were applied to the same extent in all of the centres in our study? These questions remain to be answered.

Interaction of the causal relationships with outcomes

This concerns whether an effect found in one kind of outcome (e.g. one-year survival) may hold if other outcome observations were studied (e.g. five-year survival) (136).

Regarding our first outcome, we found that both groups had a significant reduction in the use of substances from baseline to 6 and 12 months of follow-up, but that there was no significant difference in the reduction of substance use between groups. We do not know if this result would hold in the long term, e.g. after two or five years. However, the longer the timespan between the intervention received and the follow-up assessments, the more questionable the relationship between the intervention and the outcome would be as the person would be affected by many factors over the longer time span.

Our second finding was that neither group experienced a significant reduction in psychiatric symptoms. We do not know if this finding would be the same if we had used other outcome measures, for example, instruments that measure anxiety and depression more specifically. Neither do we know if the patients would have improved from psychiatric symptoms over a longer time span. Some studies suggest that change in psychiatric symptoms might take longer than the change in substance use behaviour (99).

Our third finding was that the intervention group improved significantly better than the control group with regard to motivation for treatment. We do not know if this difference would persist over a longer time span, for example, after two or five years.

6.2.5 Limitations of the designs

In this study, we used a pragmatic group randomized controlled design. The randomized controlled trial is the gold standard for investigating the effect of one intervention compared to another. One of the limitations of the RCT design is the very strict inclusion criteria that limit generalization to patients normally seen in clinical practice and the individual tailoring that is normally applied to treatment operations in clinical practice. To enhance generalization to everyday clinical practice, we used a pragmatic approach with broader inclusion criteria, narrower exclusion criteria and a less strict treatment manual (138). This enhances external validity at the expense of internal validity and makes it more difficult to infer causation from the intervention given.

We also used a multi-centre design to be able to acquire a larger sample size to enhance effect sizes. To avoid contamination of knowledge between conditions, we chose to randomize at a centre level. Randomization has the advantage that baseline differences due to known and unknown confounders are minimalized. However, when the randomization is done at centre-level, there might still be a risk of selection bias and baseline differences at the individual level. There is also a risk of nesting within centres. However, this can be accounted for by multilevel statistical analyses.

Multi-centre trials represent organizational, administrative, economic and treatment fidelity challenges that must be addressed by thorough planning and close monitoring. To address this, we

engaged one local trial administrator at each community mental health centre to run the project locally in close collaboration with the research group.

The adaptations to the RCT design were made to optimize external validity and effect sizes. However, these adaptations produced new challenges that are described and discussed in paper IV.

7. Discussion of the main results

In the following I will discuss our results in the light of other research findings.

7.1 Identifying patients with co-occurring mental and substance use disorders in community mental health centres

The main finding from our first paper was that the different approaches we used to estimate the prevalence of substance use disorders in our population of patients in community mental health centres gave estimates between 10 and 12 %, which is on a level with the 12-month prevalence observed in the general population (29, 49-54). Given the high comorbidity of mental and substance use disorders (29, 49, 55, 57, 226-228), one would expect the prevalence to be higher in this clinical population (60, 61, 229-235). By combining the different measures in our study, the prevalence of substance use disorders increased to 17 %, which is still somewhat low, but more comparable to what would be expected in a psychiatric outpatient population (229, 231-233).

A secondary finding was the poor agreement between the different measures. This is in accordance with the findings from a similar Norwegian study on psychiatric in- and outpatient clinics, which used data from the Norwegian Patient Register (236). In this study, 21% of the outpatients were classified with a "middle to high drug use", whilst only 48% of these patients were given an ICD-10 diagnosis of substance use disorder. Further, 23% of the inpatients were classified with "middle to high drug use" and only 32% of these patients were given an ICD-10 diagnosis of substance use disorder.

The low prevalence and poor agreement between measures raises the question of whether substance use disorder is adequately detected in psychiatric outpatient clinics. The issues concerning the reliability of measures, the validity of clinical diagnostic assessments and the possibility of a selection bias are discussed in chapter 6.1. Another explanation for the low prevalence rate could be lack of referrals of patients with substance use disorders to the community mental health centres. However, given the many findings of high comorbidity between substance use disorders and most mental disorders (29, 49, 55, 57, 226, 227, 234) one would expect higher prevalence rates of substance use disorder among patients with mental illnesses than in the general population. It is possible that clinicians do not give sufficient attention to the possibility of a comorbid substance use

disorder amongst patients in psychiatric treatment facilities (63, 64). Similarly, co-occurring psychiatric diagnoses are missed in addiction treatment facilities (237). These findings suggest that using clinical diagnostic measures alone underestimates the prevalence of co-occurring disorders. To address this issue, Rush et al (233) used a combined measure to estimate the prevalence in their sample in a similar way to us. Another explanation for the poor agreement between measures could be that the different instruments used measure substance use disorders over different time periods. The AUS measures alcohol use over the last six months and the DUS measures drug use over the same period. The HoNOS item 3 measures substance use during the last two weeks and the ICD-10-codes most frequently used in this material measure current substance use. However, one would at least expect the ICD-10 and the HoNOS item 3 to overlap as they investigate approximately the same time period.

Our study has several limitations. Issues concerning the validity of clinical diagnostic assessments are discussed in chapter 6.1 and underline the necessity of good screening procedures to aid diagnostic assessments (63, 64). In addition, the participation rate was quite low and varied greatly between centres. A low participation rate is quite common in clinical studies (142, 238, 239). This might be explained by the considerable workload in most clinical practices (240), misconceptions about the trial, variable interpretation of eligibility criteria, or paternalism (142). It might also depend on how well the study was implemented in the clinics (142, 241).

Despite these limitations, our findings suggest that substance use disorders are under-detected in this patient population and this is likely to result in under-treatment and delayed recovery. Mental health services need to implement systematic screening and diagnostic procedures to identify the specific problems and needs for each patient and tailor the treatment approaches accordingly. Over the years, several screening and diagnostic instruments have been developed and tested. In 2007, the Norwegian Knowledge Centre for Health Services did a systematic review of screening and diagnostic tests for substance use disorders and mental illness (242). They concluded that the AUDIT and the CAGE questionnaire (243) were the screening instruments that best identified alcohol use disorders amongst patients with severe mental illnesses, and that the Psychiatric Research Interview for Substance and Mental Disorders (PRISM) (244) is a diagnostic tool that shows good concordance with reference standards. In addition, in recent years several screening tools that show promise have been developed to detect substance use disorders in psychiatric patient populations, such as the Dual Diagnoses Screening Interview (DDSI) (245) and the DrugCheck Problem List (PL) (246). Similarly, there are several screening tools for detecting mental disorders in substance use treatment

populations. Rush et al (247) compared four such screening tools; the GAIN-short screener-Internalizing Disorder Screener (GAIN-SS IDScr) (248), the Kessler-6 (K6) (249-251), the Psychiatric Subscale of the ASI, and the Psychiatric Diagnostic Screening Questionnaire (PDSQ) (252, 253), using the SCID as the reference tool. They found that all the screening instruments performed reasonably well in detecting broad groups of mental disorders with the GAIN-SS-IDScr being the most efficient because of its shorter length.

7.2 The characteristics of patients with co-occurring mental and substance use disorders in community mental health centres

The main findings from our second paper were that in psychiatric outpatient clinics, patients with co-occurring substance use disorders differ from those without co-occurring substance use disorders in a number of ways.

Firstly, we found that the patients with co-occurring substance use disorder were more often male, less often in a relationship and more often living alone. This is largely consistent with other epidemiological and clinical studies (53, 57, 62, 69, 227, 254-256). Although, in some studies people who seek psychiatric outpatient treatment for depression or anxiety and who have a co-occurring alcohol use disorder, seem to be predominantly female (257, 258). Nevertheless, our findings suggest that people with co-occurring substance use disorders are a more vulnerable group and therapists should tailor their treatment plans accordingly.

Secondly, we found that the patients with co-occurring substance use disorders had more severe morbidity as measured with the HoNOS on five out of eleven parameters. Higher morbidity among patients with co-occurring mental and substance use disorders has been found in several studies (231, 233, 256, 259). One study, targeting patients in community mental health centres with measures comparable to our study, found that patients with schizophrenia in inpatient and outpatient clinics with co-occurring substance use disorders had higher sum-scores on the HoNOS than patients without this comorbidity (260). Another study found higher sum-scores on the SCL-90R on all sub-scores among outpatients with co-occurring schizophrenia and substance use disorder compared to patients with schizophrenia but without substance use disorders (67). It is essential that these issues are detected and addressed in the patient's treatment plan.

Thirdly, we found that the patients with co-occurring substance use disorder had lower prevalence of anxiety and depression compared to the patients without substance use disorders. This is in contrast to most studies in this field, which indicate a higher prevalence of other psychiatric diagnoses amongst patients with substance use disorders (49, 57, 254). However, a study on the prevalence of anxiety and depression amongst patients with co-occurring substance use disorders in an acute psychiatric ward had similar findings to our study (69). There are several possible explanations for this. Firstly, the different centres could have recruited different numbers of patients with and without co-occurring substance use disorders because of differences in the catchment areas. Secondly, it could be that patients with comorbid substance use disorder need less other morbidity before they are referred to the community mental health centres, i.e. competing risks (261). Thirdly, Patients with substance use disorders and co-occurring anxiety and depression might be referred to addiction treatment centres rather than psychiatric outpatient clinics. However, patients in addiction treatment centres might not receive adequate treatment for their co-occurring psychiatric disorders. According to a study by Bakken et. al., the number of and specific axis 1 and axis 2 disorders together with the severity of substance use disorder at admission were all independent predictors of a high level of mental distress at six-year follow-up (70). This underlines the need for good diagnostic and screening routines to detect such disorders, and competent staff to treat these conditions in an integrated way.

Our fourth finding was that the patients with co-occurring substance use disorders in these community mental health centres were treated differently than those without substance use disorders, i.e. they received less outpatient treatment and they were treated at too low a competency level according to the therapists. One explanation might be that the therapists feel they lack the competence or the resources to treat these patients in an outpatient setting. This view is in accordance with studies of clinicians in mental health centres who report that they feel unprepared and lack knowledge of patients with dual diagnosis (262, 263). This is also in line with studies which describe difficulties in implementing new knowledge and treatment guidelines for patients with co-occurring mental and substance use disorders in mental health care (222-224, 264).

Finally, we found poorer outcomes with regard to recovery from psychological symptoms as well as poorer outcomes at a borderline significance level for three of the remaining six items among the patients with co-occurring substance use disorder compared to the patients without comorbidity. This is in line with previous findings of poorer treatment outcomes for this group of patients (75), and

in accordance with our other findings that these patients have greater morbidity and receive less adequate help for their problems.

There are several limitations to our study. The issues concerning fishing related problems, the reliability of measures, the validity of clinical diagnostic assessments, and adequate explication of constructs are discussed in chapter 6.1. The representativeness of outpatient clinics in Norway might also be questioned, both with regard to prevalence rates, the substances used in the catchment areas and the clinical routines in the community mental health centres. These findings should be confirmed with further studies, preferably with comparable measures between studies, e.g. screening instruments like the AUDIT and the DUDIT, structured diagnostic interviews like the SCID or the PRISM, measures for the severity of psychosocial symptoms or distress like the HoNOS or the SCL-90 and a systematic measure for evaluating the use of substances like the ASI.

7.3 The effectiveness of integrated treatment among patients with substance use disorders co-occurring with anxiety and/or depression in community mental health centres

Our first finding was that both treatment conditions showed a decline in the use of alcohol and other substances as measured by the AUDIT, the DUDIT, and the EuropASI. This could indicate that both interventions were effective in reducing the use of substances and that receiving treatment is more important than the type of treatment. It could also be an effect of the assessments and thereby blurring experimental contrast (265, 266), or it could be a case of “regression to the mean” (197, 198). Additionally, it could be the result of a type 2 statistical error as our sample size is quite small. A recent systematic review from 2012 looking at the effect of integrated treatment among people with substance use disorders and co-occurring anxiety and/or depression found that motivational interviewing and cognitive behaviour therapy were associated with significant reductions in alcohol consumption (267). The use of integrated treatment for alcohol and depression with cognitive behavioural therapy as the main treatment modality has also shown a greater reduction in the use of alcohol than treatment as usual (119, 268, 269). Similarly, a study that used motivational interviewing to treat substance use among outpatients with depression showed a significant reduction in hazardous drinking in the intervention group (257).

Our second finding was that none of the groups experienced a reduction in psychiatric symptoms. This might be explained by the relatively short follow-up period. A review from 2008 found improvements in mental health in the long term when motivational interviewing was combined with cognitive behaviour therapy (270) which could mean that these changes might occur later in the course of treatment. Other possible explanations could be that the SCL-90r is not sensitive to small changes or that the material is too small to produce sufficient effect sizes, i.e. type 2 statistical error. A review from 2012 looking at psychological interventions for patients with alcohol misuse co-occurring with depression or anxiety disorders, found that a combination of motivational interviewing and cognitive behavioural therapy was associated with significant reductions in alcohol consumption and depressive and/or anxiety symptoms (267). Similarly, a review from 2014 regarding integrated treatment of comorbid major depression and alcohol use disorder with cognitive behavioural therapy and motivational interviewing as the main treatment modalities showed small, but significant, effects both in decreasing alcohol consumption and depressive symptoms, compared to the control conditions (271).

Our final finding was that the intervention group improved significantly in motivation for treatment compared to the control group even though we failed to find a reduction in the actual use of substances. One study on patients with psychosis and substance use disorders using integrated motivational interviewing and cognitive behavioural therapy had similar findings as our study; the interventions did not improve outcome in terms of hospitalization, symptom outcomes, or functioning, but did improve the patients' motivation to change their substance use (272). It could be that the motivation for change occurs before the actual change in behaviour. Several studies have shown that interventions that include motivational interviewing as one of the therapeutic modalities have a positive effect on the patient's motivation for treatment and changing addictive behaviours (270, 273). Even a motivational intervention as brief as a one-hour session made a positive shift in the stages of change among opiate users at a methadone clinic compared to the control group (274).

Our study has several limitations. Issues concerning the possibilities of a selection bias and insufficient implementation of the intervention have been discussed in chapter 6.2 together with the possibility of low statistical power. The problem of low statistical power is quite common in clinical trials as most randomized clinical trials fail to enrol the target number of patients during the inclusion period (143, 273). This is even more pronounced in research involving people with substance use disorders as they commonly have high rates of attrition from both treatment and clinical trials (147, 148, 275). In two reviews on integrated psychosocial interventions for patients with substance use

disorders and co-occurring anxiety and depressive disorders, many of the studies included had small sample sizes (123, 271). Further, our study had no special focus on psychopharmacological treatment. If such treatment differed between groups it would alter the results. However, the clinicians in all the centres are obliged to deliver evidence-based treatment for each condition including psychopharmacological treatment. This is in line with our intention of tailoring the treatment to the patients need by using a broad array of therapeutic modalities. As the patients were classified as completers if they had met for as few as five sessions, one could argue that the trial mainly measures the effectiveness of motivation. On the other hand, the majority of patients in both groups received 10 sessions or more. Baker et al (276) found that a 10-session intervention was associated with better improvement in depression and global functioning than a one session brief intervention. However, such complex conditions might need longer treatment and observation time than the one-year follow up that this and most clinical trials have. Larger studies with a longer follow-up time will be needed to judge whether this intervention is cost-effective given the extra training needed to deliver it.

7.4 Lessons and adaptations in research involving psychosocial interventions for patients with co-occurring mental and substance use disorders

This study illustrates common challenges in conducting pragmatic multi-site group randomized clinical trials with complex interventions in a non-selected clinical population. Different strategies to overcome these challenges are discussed.

Our first challenge was to recruit centres and motivate their participation regardless of which treatment condition they would be allocated to. This process illustrated the importance of involving the participating centres at an early stage in the planning of the study both to enhance their feeling of “ownership” of the study, and to develop a design that is appropriate to the clinics’ needs and workload. Strong reinforcement strategies have shown to be essential to make the effort worthwhile regardless of allocation (238, 277). One reinforcement strategy could be to give the co-workers at the centres a role that fulfils the Vancouver requirements for co-authorship (277).

Our second challenge was that the local trial administrators were a mix of people with different education, training, interests, motivation, and time available for the trial. This made it challenging to

secure data quality and adherence. Several studies have shown that securing adherence is a complex issue that requires multiple and comprehensive strategies at different stages of the trial (278, 279) together with direct involvement from the researchers at each centre (222, 280, 281). One strategy could be to visit each centre regularly, at least once a month, to ensure data-quality and uniformity in data collection between centres.

A third challenge was that the therapists did not comply with the screening routines of the study. This might be explained by heavy workload, difficulties in thematizing substance misuse and lack of support from the clinics' management. The implementation of new routines and treatment methods has long shown to be a challenge in most settings and require formidable resources on many levels (145, 222, 224, 280). Ideally, such routines should be well established before the start of the study (277).

A fourth challenge was the different referral policies between centres. Because of new national guidelines, these policies were changed during the planning phase of the trial and affected the number of eligible patients. This shows that one needs to be aware of policies (formal and informal) and organizational changes and take them into consideration when planning a study.

A fifth challenge was that only a low percentage of the patients who screened positive for substance use disorders were actually referred for further assessments to be included in the trial. The main reason was lack of consent from the patients. This could have reflected how the study was presented to the patients by the therapists, maybe reflecting the therapist's own attitudes towards the project (222, 282). It could also be explained by how comfortable or uncomfortable the therapists felt in addressing the issue of substance abuse with the client. If so, it underlines the need of extra coaching in dealing with this matter (224, 263, 283-287). Again this emphasizes the need to involve the centres at an early stage of the project planning, to ensure a feeling of "ownership" towards the study, to make sure that the centres' management is supportive and that they encourage their therapists to comply with the demands of the study. Several studies state that a prerequisite for successful implementation of a trial into a clinical setting is a supportive clinical management that motivates the clinicians to participate (222, 224, 280).

A sixth challenge was the slow and, ultimately, low inclusion rate. In our experience, extending the inclusion period did not increase the numbers to a great extent. This emphasizes the importance of focusing all efforts and resources on the original recruitment period when the clinicians and centres

are still fully focused on this task. This also minimizes the risk of therapist turnover and other additional costs (142, 281, 288, 289).

Our seventh and last challenge was to encourage patients to return for the follow-up assessments. Our experience is that the local trial administrators who put more effort into the task than was expected of them and who were the most creative managed to reach the most patients for their follow-up assessments. This underlines the fact that this type of research puts heavy demands on the participating centres and local trial administrators, and that these demands and costs are often underestimated (224, 281).

8. General conclusions

There is mounting literature on the high prevalence of substance use disorders and of comorbidity between mental and substance use disorders in clinical populations. However, our study provides strong evidence that this is still unrecognized in clinical practice. The study also raises questions about the reliability of the AUS, the DUS and the HoNOS when used in a busy clinical setting. At the very least, it suggests that regular monitoring and training is a prerequisite of their clinical use.

We found that outpatients with substance use disorders were more frequently male, single, and living alone, had a higher level of morbidity, less anxiety and mood disorders, less outpatient treatment and had less improvement in regard to recovery from psychological symptoms compared to patients with no substance use disorder. This means that the community mental health centres need to implement systematic screening and diagnostic procedures, preferably with validated measures, in order to detect patients with substance use disorders, to tailor the treatment to the special needs of these patients, and improve recovery.

Our second study shows that integrated treatment is effective in increasing motivation for treatment among patients with anxiety and/or depression co-occurring with substance use disorders in outpatient clinics.

Studies of complex interventions in unselected clinical populations are essential in the development of evidence-based treatments in the psychiatric and addiction field. The methodological problems are considerable but it is possible to overcome these challenges by thorough planning and by addressing the obstacles at an early stage.

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Errata

Page 6, paragraph 2, line 3: the OR of 2.8 is corrected to 2.6

This error is repeated in paper I, page 1, column 2, line 2.