Benzodiazepines and antipsychotics in severe mental illness

Optimizing and characterizing prescribing practice

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Preface

The work included in this doctoral dissertation was conducted mainly during my postdoc position at Centre for Neuropsychiatric Schizophrenia Research, Mental Health Centre Glostrup, from 2011-2015. The studies were planned as a consequence and necessary follow-up on some of the results in my Ph.D. thesis which was defended in January 2010.

First and foremost, I have to thank all the patients who managed to withdraw from decades of benzodiazepine use during their participation in the SMART trial. It was very encouraging to experience the energy devoted to the process by most of the participants.

Furthermore, I would like to thank my colleagues and co-workers at Centre for Neuropsychiatric Schizophrenia Research for collaboration on the trial and practical help in trial procedures and tests. In particular, I cordially thank Professor Birte Glenthøj for always supporting my ideas and ambitions and giving an incredible effort to make things happen.

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Contents
1. List of publications included in the thesis ................................................................. 5
2. General introduction .................................................................................................. 7
   2.1 Benzodiazepines ..................................................................................................... 7
   2.2 Antipsychotics ........................................................................................................ 10
   2.3 Severe mental illness .............................................................................................. 11
   2.4 Summary of previous results setting the scene ......................................................... 11
      2.4.1 Antipsychotic-benzodiazepine co-prescribing .................................................. 12
      2.4.2 Antipsychotic polypharmacy ......................................................................... 13
3. Aims and hypotheses .................................................................................................. 14
4. The SMART trial: Discontinuation of benzodiazepines using melatonin in patients with severe mental illness (papers 1-6) ................................................................. 16
   4.1 Introduction ........................................................................................................... 16
      4.1.1 Background for investigating neurocognitive performance, subjective well-being and psychosocial functioning ............................................................... 16
      4.1.2 Background for sleep examinations ................................................................ 17
   4.2 Methods and materials ......................................................................................... 20
      4.2.1 Eligibility criteria ............................................................................................. 20
      4.2.2 Benzodiazepine taper procedure and clinical assessments .............................. 21
      4.2.3 Outcomes ........................................................................................................ 22
      4.2.4 Specific procedures and measures .................................................................... 23
   4.3 Results .................................................................................................................... 25
      4.3.1 Main results (paper 2) ..................................................................................... 25
      4.3.2 Neurocognitive performance, subjective well-being and psychosocial functioning (paper 3) .................................................................................................... 27
      4.3.3 Objective and subjective sleep quality (Paper 4) ............................................. 29
      4.3.4 Circadian rest-activity rhythms (paper 5) ....................................................... 30
      4.3.5 Sleep spindle activity and morphology (paper 6) ............................................. 31
   4.4 Discussion ............................................................................................................... 32
5. Cochrane Review: Pharmacological interventions for benzodiazepine withdrawal (papers 7-8) ................................................................. 34
   5.1 Introduction ........................................................................................................... 34
   5.2 Methods and materials ......................................................................................... 34
   5.3 Results .................................................................................................................... 35
   5.4 Discussion ............................................................................................................... 35
6. Observational studies: Different aspects of antipsychotic prescribing using register data .................................................................................................................. 39
   6.1 Antipsychotic polypharmacy and health service costs (paper 9) .......................... 39
1. **List of publications included in the thesis**

Listed in order of subject of interest and study design


None of the above papers or results herein has previously been submitted with the intention of acquiring an academic degree.
2. General introduction

2.1 Benzodiazepines

Benzodiazepines are licensed for short-term treatment of severe anxiety or insomnia not responding to non-pharmacological interventions [1]. Though initially effective, tolerance as well as psychological and physical dependence may develop within few weeks of treatment. Dependence develops in about half of benzodiazepine users after one month of treatment with increased risk in individuals with higher doses, longer duration of use, concomitant use of other psychotropics, higher age, a history with mental illness, and the use of short-acting agents with high potency [2,3,4]. Tolerance (i.e. the tendency to lose efficacy over time and thus a necessity to increase the dose to maintain clinical effect) as a sign of dependence may develop within few weeks of treatment, most pronounced to the sedating effect while evidence suggests that not all individuals develop tolerance to the anxiolytic effect [5,6,1,7]. Benzodiazepines are indicated mainly for primary anxiety and insomnia but in psychiatric populations benzodiazepines are often co-prescribed with other psychopharmacological agents to treat secondary anxiety and insomnia, i.e. symptoms that are part of the primary psychiatric illness.

A substantial number of different benzodiazepine compounds exist, differing mainly in duration of elimination half-life but also with differences regarding lipid solubility explaining different rates of passage of the blood-brain barrier. Based on elimination half-life, benzodiazepines are somewhat arbitrarily divided into anxiolytic benzodiazepines (with longer half-life) and hypnotic benzodiazepines (with shorter half-life). Benzodiazepines are allosteric modulators of the GABA A (γ-aminobutyric acid, type A)-receptor. The GABA A-receptor has binding sites for its main agonist, GABA, and for benzodiazepines (as illustrated in Figure 1). GABA A-receptors are heteropentamers made up from 19 known subunits (α1–6, β1–3, γ1–3, δ, ε, θ, ϖ and ρ1–3) with a central chloride channel [8,9]. Animal studies using genetically modified mice have demonstrated that α1-containing GABA A-receptors are responsible for the sedative, anterograde amnestic and partly the anticonvulsant properties of benzodiazepines; α2-containing GABA A-receptors for the anxiolytic action; and α3- and α5-containing GABA A-receptors for the muscle relaxant action [8]. When a benzodiazepine binds to the receptor it changes allosterically thus increasing its affinity for GABA. This will allow a higher influx of chloride ions leading to the clinical effects of general inhibition throughout the central nervous system, giving rise to the anxiolytic, sedating, seizure suppressing and muscle-relaxing effects.
Figure 1: Pharmacologic characteristics of GABA A-receptors. The GABA A-receptor consists of five transmembrane glycoprotein subunits arranged around the central chloride channel. Each subunit is composed of four domains. Benzodiazepines increase the affinity of the GABA A-receptor for GABA and the likelihood that the receptor will open for chloride ions (light blue). 

Figure and adapted legend reprinted from Soyka M. N Engl J Med 2017;376:1147-1157. Reproduced with permission from (scientific reference citation), Copyright Massachusetts Medical Society.

Benzodiazepines are subjectively well-tolerated and associated with a low risk of toxicity. The so called z-drugs or benzodiazepine-like drugs comprise a similar but not quite identical group of drugs having selective affinity for GABA-A-receptors containing an α-1 subunit whereas ‘true’ benzodiazepines bind non-selectively to GABA A-receptors independent of type of subunit [10]. Due to this selectivity, the z-drugs are only indicated for insomnia since they do not share with the benzodiazepines other clinical effects than sedation (except when used in excessive doses). Post-marketing it has become clear that the z-drugs are as prone to development of dependence as the ‘true’ benzodiazepines because this side effect is linked to exactly the α-1 subunit. Apart from tolerance and dependence issues, the main disadvantages of treatment with benzodiazepines include: sedation, ‘hang-over’ effects the next day, cognitive dysfunction (impaired concentration, memory and attention), symptom rebound after discontinuation, increased risk of traffic accidents due to impaired driving abilities, and increased risk of falls and fractures [9]. After more than a few weeks of treatment, gradual discontinuation is recommended due to the risk of withdrawal symptoms as summarized in Table 1. Withdrawal symptoms will typically appear within 2-3 days after cessation of short-acting benzodiazepines and within 5-10 days after cessation of longer-acting agents [9].
### Table 1: Clinical symptoms and complications of benzodiazepine withdrawal

<table>
<thead>
<tr>
<th>Psychopathologic symptoms</th>
<th>Vegetative symptoms</th>
<th>Neurologic and physical complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased anxiety</td>
<td>Trembling</td>
<td>Increased risk of seizures</td>
</tr>
<tr>
<td>Nervousness</td>
<td>Sweating</td>
<td>Impairment of voluntary movements</td>
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<tr>
<td>Sleep disorders</td>
<td>Nausea and vomiting</td>
<td>Cognitive impairments</td>
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<tr>
<td>Inner restlessness</td>
<td>Motor agitation</td>
<td>Impairment of memory</td>
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<tr>
<td>Depressive symptoms</td>
<td>Dyspnœa</td>
<td>Perceptual impairments</td>
</tr>
<tr>
<td>Irritability</td>
<td>Increased heart rate</td>
<td>Hyperacusis</td>
</tr>
<tr>
<td>Psychosis-like conditions, delirium</td>
<td>Elevated blood pressure</td>
<td>Photophobia</td>
</tr>
<tr>
<td>Depersonalization, derealisation</td>
<td>Head aches</td>
<td>Hypersonomnia</td>
</tr>
<tr>
<td>Confusion</td>
<td>Muscle tension</td>
<td>Dysesthesia, kinaesthetic disorders, muscle twitching and fasciculations</td>
</tr>
</tbody>
</table>

The neural origin of the addictive nature of benzodiazepines is similar to that of other drugs of abuse: it has been shown in animal studies that benzodiazepines increase firing of dopamine neurons of the ventral tegmental area through modulation of α-1 containing GABA-A receptors in nearby interneurons [11]. Thus, dependence on benzodiazepines develop due to dopaminergic activity in the reward circuits of the brain leading to drug reinforcement and eventually drug seeking behaviour. The effect of benzodiazepines in the reward system is shown in Figure 2.
Figure 2: The neural origin of addiction with use of benzodiazepines. When benzodiazepines bind to α1-containing GABA A-receptors on GABAergic ventral tegmental area neurons this leads to inhibition of these cells and reduced release of GABA. This results in a disinhibition (=activation) of the dopaminergic VTA neurons resulting in increase in dopamine release in the ventral striatum. Figure and adapted legend reprinted from Rudolph U and Knoflach F. Nature Reviews 2011;10:685-697. Reprinted with permission from the publisher.

The neural origin for development of tolerance is not known in details but is generally being understood as neuroadaptive mechanisms that take place as response to chronic benzodiazepine exposure. The fact that tolerance is not developed equally to all the clinical actions of benzodiazepines suggests that several adaptive mechanisms might contribute including adaptations in the GABA A-receptor, intracellular mechanisms, or changes in other neurotransmitter systems including the glutamatergic system [12]. Tolerance and withdrawal symptoms are thought to represent the same underlying neuroadaptive processes with withdrawal symptoms appearing when the compensating effect of benzodiazepines is lacking [12].

2.2 Antipsychotics

Antipsychotics are licensed for the treatment of psychotic disorders, mainly schizophrenia spectrum, and as mood stabilizers in bipolar affective disorder. Antipsychotics are associated with a long list of potentially serious and
potentially irreversible side effects and therefore prescribing practices not following general recommendations are worrying. Antipsychotics comprise a heterogeneous group of agents but all displaying their antipsychotic action mainly through antagonistic effect on the dopamine D2-receptor. Side effects directly attributable to D2-receptor blockade comprise extrapyramidal symptoms (Parkinsonism, dyskinesia, dystonia and akathisia), secondary negative symptoms and hyperprolactinemia (oligomenorrhea/amenorrhea, gynecomastia, galactorrhoea, decreased libido, infertility, osteopenia) [13,14]. In addition, antipsychotics work as antagonists on a range of other receptors with implications for their side effect profile. Additional receptor blockade (with resulting clinical side effects) include (but is not limited to) antihistaminergic (sedation, weight gain), anticholinergic (confusion, cognitive impairment, constipation, dry mouth, urinary retention, blurred vision), alfa-adrenergic (orthostatic hypotension, nasal congestion, oedema) and 2C serotonergic (weight gain) [13,14].

2.3 Severe mental illness

Definitions of severe (or serious) mental illness vary depending on whether the term is used for legal, clinical or epidemiological purposes [15]. As defined by US federal regulation, severe mental illness is the presence of at least one DSM-defined mental disorder that leads to substantial interference with one or more major life activities. In clinical practice, mental disorders that will typically fulfil criteria for severe mental illness include schizophrenia, schizoaffective disorder, bipolar disorder, and borderline personality disorder [15]. According to definitions by the UK National Institute of Clinical Excellence, severe mental illness comprises mainly psychosis and bipolar disorder (https://www.nice.org.uk/sharedlearning/improving-physical-health-for-people-with-serious-mental-illness-smi) and this is the understanding of the term that is used in this thesis.

2.4 Summary of previous results setting the scene

As part of my Ph.D. thesis [16], we published a population based nested case-control study examining the association of polypharmacy with risk of death from natural causes in 27633 outpatients with schizophrenia [17]. We found that antipsychotic polypharmacy, i.e. concomitant treatment with more than one antipsychotic drug, was not associated with increased mortality compared with antipsychotic monotherapy. We also examined the risk of death from natural causes using concomitant treatment with antipsychotics and benzodiazepines and found that the risk of death was increased with almost 80% (OR 1.78, 95% CI 1.25-2.52) when outpatients with schizophrenia had been treated with a combination of at least one antipsychotic drug and at least one benzodiazepine during the last three months before the
date of death. These findings have been corroborated by similar findings from Tiihonen et al. using first Finnish [18] and subsequently Swedish [19] register data resembling the Danish ones. Tiihonen et al. found that antipsychotic-benzodiazepine combination treatment was associated with increased non-suicidal deaths in both Finnish (HR 1.60; 95% CI 0.86-2.97) [18] and Swedish (all-cause mortality: HRs up to 1.74; 95% CI 1.50 to 2.03) [19] cohorts (N=2588 and N=21492, respectively) of patients diagnosed with schizophrenia. Likewise, Tiihonen et al. replicated our finding of no excess risk of death in schizophrenia patients treated with antipsychotic polypharmacy compared with monotherapy [18]. Recently, a US study using Medicaid claims data and death certificate data from 18953 patients with schizophrenia reported similar findings with excess risk of all-cause mortality (HR 1.48; 95% CI 1.15-1.91) and natural cause mortality (HR 1.33; 95% CI 1.10-1.75) associated with antipsychotic-benzodiazepine combination treatment [20]. Limitations of register based observational studies include that causality cannot be claimed due to risk of residual confounding. However, risk of death in association with certain pharmaceutical agents cannot be assessed by other means and the findings indicate that combining antipsychotics and benzodiazepines may set the individual at risk of increased mortality. This is not an acceptable premise given the lack of evidence of therapeutic advantages of this combination treatment.

The two other studies in my Ph.D. thesis were also concerned with polypharmacy investigating 1) organizational predictors of antipsychotic polypharmacy [21] and 2) an educational intervention to reduce the frequency of antipsychotic co-prescribing [22]. As such, the results from my Ph.D. thesis set the scene for the studies included in this doctoral dissertation which, of course, also relate to a broader context and therefore a brief overview of antipsychotic-benzodiazepine co-prescribing and antipsychotic polypharmacy is provided below.

### 2.4.1 Antipsychotic-benzodiazepine co-prescribing

Antipsychotic-benzodiazepine co-prescribing is common clinical practice in the treatment of psychosis and is well-established and well-tolerated in the acute phase of psychotic exacerbations with an immediate need of sedating and anxiolytic effects, and frequently also a need to reduce aggression and psychomotor agitation [23,24,25]. However, long-term antipsychotic-benzodiazepine co-treatment in severe mental illness is not supported by any evidence and should be regarded with at least the same worry and concerns as chronic treatment with benzodiazepines in isolation. Efficacy of benzodiazepines for schizophrenia symptoms was investigated in a Cochrane review where no beneficial effect was recorded except for the acute sedative effect observed within the first 30-60 minutes of treatment [26]. As
described above, recent evidence points to the fact that antipsychotic-benzodiazepine co-treatment might be associated with an increased risk of natural death which further ads to the list of serious disadvantages associated with long-term prescribing of this combination regimen. A recent magnetic resonance imaging study of patients with schizophrenia medicated with both antipsychotics and benzodiazepines found that benzodiazepine use is associated with volume decrease in the caudate nucleus indicating a need for future studies on associations between brain volume and antipsychotic medication to be sure to adjust for concomitant benzodiazepine use [27].

2.4.2 Antipsychotic polypharmacy

Antipsychotic polypharmacy, i.e. concomitant treatment with two or more different antipsychotic compounds, is common practice in psychotic patients and has been extensively described and debated, especially in relation to schizophrenia. Reasons for prescribing antipsychotic polypharmacy include insufficient treatment response on monotherapy (regarding psychotic symptoms and/or negative symptoms or cognitive dysfunction), an aim to reduce side effects of ongoing treatment, and being trapped on polypharmacy during a process of cross-titration switch from one antipsychotic compound to another [28]. Disadvantages associated with antipsychotic polypharmacy include an increased burden of side effects (including metabolic side effects when using low-dose quetiapine), reduced adherence, higher total antipsychotic dose, risk of unwanted drug-drug interactions, increased risk of medication errors, and difficulties ascribing specific effects/side effects to a specific antipsychotic agent [29,30,31,32,33,34].

A number of systematic reviews and meta-analyses have been performed since 2007 [35,36,37,38,39,40,41,42,43]. The conclusions from these reviews/meta-analyses are quite uniform: antipsychotic polypharmacy does not seem to be more efficacious than antipsychotic monotherapy, but conclusions are limited by small studies of poor quality. The meta-analyses published from 2007-2009 found that there might be one exception, namely the subpopulation of treatment resistant patients with insufficient response to clozapine where an additional antipsychotic compound in combination with clozapine resulted in a small-moderate increase in efficacy [36,37,40,43]. These findings are reflected in national and international clinical guidelines which recommend antipsychotic monotherapy with several different antipsychotics including clozapine before thinking of adding another antipsychotic drug [44,45,46,47]. The reviews/meta-analyses published after 2009 cannot replicate the possible positive findings for augmenting clozapine treatment with another antipsychotic compound in treatment resistant schizophrenia [35,38,39,41,42]. However, in the most recently published meta-analysis, there was one significant finding: a beneficial effect on negative symptoms specific for aripiprazole
augmentation compared with monotherapy with a small effect size (8 studies, N=532, SMD -0.41, 95% CI -0.79 to -0.03) [38]. Furthermore, aripiprazole augmentation was associated with reduced prolactin levels and body weight [38]. The evidence base summarized above is derived from studies mainly including subjects with schizophrenia but remains unstudied as regards other psychiatric disorders. In disorders with lack of evidence of therapeutic efficacy (i.e. off-label prescribing) the use of antipsychotic polypharmacy will per definition be associated with an even worse risk-benefit ratio than in schizophrenia.

3 Aims and hypotheses

The aims of this thesis were directly driven by the results summarized above from my Ph.D. thesis and included

A. Investigating pharmaceutical agents, in particular melatonin, to facilitate benzodiazepine withdrawal. Long-term benzodiazepine treatment is associated with considerable risks and detailed knowledge on how to optimise the discontinuation process is clearly needed. Based on current knowledge of the effects of melatonin, this agent is a potentially effective candidate to facilitate benzodiazepine withdrawal.

B. Examining the feasibility and safety of discontinuing benzodiazepines in patients with severe mental illness. Patient with severe mental illness might be more vulnerable to relapse/deterioration in relation to withdrawal syndrome and rebound insomnia when discontinuing benzodiazepines. Knowledge on clinical parameters when discontinuing benzodiazepines particularly in this patient population is therefore needed.

C. Investigating if the increasing societal use of antipsychotics, including polypharmacy, is justified in terms of diagnosis and prognosis. The increasing use of antipsychotics and combinations hereof for non-psychotic conditions might pose a considerable societal problem and needs further investigation.

The following specific hypotheses were tested in different study designs:

1. Melatonin accelerates benzodiazepine tapering in patients with severe mental illness. Evaluated in the SMART trial: a randomized controlled trial (protocol: paper 1, main results: paper 2).

2. Melatonin reduces benzodiazepine withdrawal symptoms in patients with severe mental illness. The SMART trial (paper 2).

3. Melatonin improves cognition after benzodiazepine discontinuation in patients with severe mental illness. The SMART trial (paper 3).
4. Melatonin increases sleep efficiency and subjective sleep quality after benzodiazepine discontinuation in patients with severe mental illness. The SMART trial (paper 4).
5. Melatonin improves sleep-wake rhythmicity after benzodiazepine discontinuation in patients with severe mental illness. The SMART trial (paper 5).
6. Benzodiazepine discontinuation in patients with severe mental illness is associated with improvement in neurocognitive functioning, increased quality of life and subjective well-being, normalization of sleep continuity and sleep architecture, improvement in social functioning, and risk of destabilization of sleep-wake regulation. These results are derived from the SMART trial comparing pre to post tapering data. These sets of results are thus not derived from the randomised controlled design and should be interpreted more cautiously. Nevertheless, they contribute with important knowledge on the overall tolerability of benzodiazepine discontinuation in patients with severe mental illness. Reported in papers 3-5.
7. Neurocognitive performance prior to benzodiazepine tapering is associated with sleep spindle activity and morphology in medicated patients with schizophrenia. Baseline data from the SMART trial (paper 6).
9. Antipsychotic polypharmacy is not cost-effective compared with monotherapy. Evaluated in a prospective cohort study combining clinical and register data (paper 9).
10. Incident use of antipsychotic drugs, including polypharmacy, is often off-label and associated with poor outcome. More specifically, we hypothesized that use of mental health care services and time to first hospitalization is associated with antipsychotic combination regimen. Evaluated in a population-based cohort study using register data (paper 10).
11. Incident use of antipsychotic drugs, including different antipsychotic polypharmacy prescribing practices, is associated with worsened occupational abilities. More specifically, we hypothesized that duration of well-fare payments, time to leaving the labour market, and increment in gross income is associated with antipsychotic combination regimen. Evaluated in a population-based cohort study using register data (paper 11).
4 The SMART trial: Discontinuation of benzodiazepines using melatonin in patients with severe mental illness (papers 1-6)

4.1 Introduction

This study is a randomized controlled trial investigating if temporary treatment with melatonin facilitates the discontinuation of long-term benzodiazepine use in patients with schizophrenia or bipolar disorder. Benzodiazepines are frequently co-prescribed with antipsychotic agents in patients with severe mental illness but no evidence base of such prescribing pattern exists. On the contrary, patients chronically treated with benzodiazepines might experience a long list of potentially serious side effects as summarized above. The reasons for choosing melatonin as the experimental compound were manifold including a potential to shorten sleep latency, reduce nightly awakenings, stabilize circadian sleep-wake rhythmicity (and via theses potential actions reduce benzodiazepine withdrawal symptoms), and a possible pro-cognitive effect [48,49]. Further contributing were documentation in the literature that patients with schizophrenia and bipolar disorder show reduced or abnormally timed endogenous melatonin secretion [49,50,48], and evidence that benzodiazepines suppress the natural secretion of melatonin [51,52]. The trial protocol (paper 1) was published before enrolment began. It should be noted that the trial was designed to include only patients with schizophrenia because this was the natural consequence of our previous results on mortality associated with benzodiazepine treatment in patients with schizophrenia. However, due to recruitment difficulties we decided to broaden the inclusion criteria to include individuals with bipolar disorder (only euthymic patients). Patients with schizophrenia and bipolar disorder share many features, can be difficult to differentiate clinically, and several authors advocate that perhaps these disorders should be considered along a psychosis spectrum rather than as two discrete disease entities [53]. Thus, for the purpose of this trial we considered it completely valid to apply a somewhat transdiagnostic approach and include patients from both diagnostic groups. The acronym SMART is short for Schizophrenia Melatonin-Associated Reduction of benzodiazepine Treatment.

4.1.1 Background for investigating neurocognitive performance, subjective well-being and psychosocial functioning

It is well-known that the acute effects of benzodiazepines include deterioration of cognitive abilities [54,55], but lately
it has also become evident that chronic use of benzodiazepines is associated with long-term negative cognitive effects [56,57] including an increased risk of developing dementia [58,59,60,61]. Hitherto, it has been unclear if benzodiazepine-related cognitive dysfunction is reversible after cessation of benzodiazepine treatment [62].

Melatonin has been praised for a range of potentially positive effects, one of them being a possible pro-cognitive effect due to anti-inflammatory actions [48]. Recently, evidence has accumulated that patients with schizophrenia have, in general, increased activity in their immune system and it has been suggested that inflammation is an important contributing factor in the complex pathogenesis behind schizophrenia including the core feature of cognitive impairment [63]. Thus, we examined the difference between the two intervention groups to investigate if melatonin improved cognitive function compared with placebo during benzodiazepine tapering. And we examined any difference in cognitive function from baseline to follow-up to investigate if benzodiazepine tapering might be associated with increased cognitive performance. To check whether trial participation, and more specifically benzodiazepine discontinuation, affected subjective well-being and psychosocial functioning, we included measures of these outcomes. Many patients and some caregivers still view chronic benzodiazepine treatment as potentially beneficial and fear deterioration of general functioning and well-being when discontinuing the treatment. Thus, we found it important to document any changes in these measures during the taper process.

4.1.2 Background for sleep examinations

Many patients and caregivers worry about the risk of worsening of insomnia when withdrawing from long-term benzodiazepine treatment. Sleep-wake regulation is more often than not disrupted in patients with severe mental illness [64,65,66,67,68]. It has been reported than up to 80% of patients diagnosed with schizophrenia suffer from sleep disturbances ranging from reversed sleep-wake cycles to a highly fragmented sleep-wake pattern [69]. Disturbances in sleep continuity parameters most often reported in schizophrenia include reduced sleep efficiency, reduced total sleep time and increased sleep latency [65,69]. Regarding sleep architecture in patients with schizophrenia, reports of reduced slow wave sleep, altered rapid eye movement (REM) sleep density and reduced REM sleep latency prevail [69,67,70]. A recent meta-analysis of sleep in schizophrenia patients compared with healthy controls found shorter total sleep time (mean total sleep time 42 minutes shorter in schizophrenia, effect size 0.76), longer sleep onset latency (31 minutes longer in schizophrenia, effect size 1.11), more wake time after sleep onset (30 minutes longer total awake time in schizophrenia, effect size 0.80), lower sleep efficiency (reduced with 10 percent points in schizophrenia, effect size 0.96), and decreased slow wave sleep and duration and latency of REM sleep [71]. However, results were
heterogeneous attributable to differences in clinical factors including illness duration, medication status and duration of medication withdrawal [71]. Disturbances in sleep continuity parameters are found in antipsychotic-naïve patients as well whereas differences in sleep architecture compared with healthy controls are not as pronounced [71]. A standard hypnogram for a young healthy adult showing regular cycles of REM and non-REM sleep is given for comparison in Figure 3.

![Figure 3: Standard hypnogram for a young healthy adult](image)

Black bars: periods of REM sleep
Grey bars: periods of non-REM sleep (stages 3-4 = slow wave sleep)

In bipolar affective disorder, prevalence and significance of sleep disturbances depend on the phase of the disorder with notably shortened sleep length being a marker of manic relapse [72]. However, evidence is accumulating that most phases of bipolar disorder are cross-sectionally associated with sleep and/or circadian rhythm abnormalities and that a close link exists between sleep disruptions and emotion dysregulation [73,72].

Sleep disturbances are a highly relevant transdiagnostic biomarker for severe mental illness because sleep disturbances of various kinds reflect disruptions in neurotransmitter functioning and functional connectivity in various brain circuits. Thus, it is not a question of viewing sleep disturbances as secondary to severe mental illness; instead, sleep disturbances reflect the core neurobiological deficits/disturbances that ultimately lead to the phenomenological presentation of mental illness [74].

Melatonin is a hormone that is secreted from the pineal gland during darkness and plays important part in promoting and maintaining sleep as well as in regulating the circadian sleep-wake cycle [48]. The sleep promoting and sleep-wake rhythm regulating actions of melatonin are mediated through its effect on melatonin receptors in the suprachiasmatic nucleus of the hypothalamus [75]. Thus, we hypothesised that melatonin might improve sleep efficiency (proportion of time in bed spent sleeping) during benzodiazepine taper.
Benzodiazepines affect sleep architecture by inhibiting slow wave sleep and REM sleep, and by increasing stage 2 (N2) sleep [76,77]. These are sleep abnormalities that are already present in patients with severe mental illness, e.g. schizophrenia [64,69,70], and thus benzodiazepines potentially aggravate inherent sleep disturbances. We examined whether these benzodiazepine induced sleep architectural abnormalities were reversible after benzodiazepine withdrawal.

In addition, we examined the rest-activity cycle using actigraphy to evaluate if melatonin had any stabilizing effect on circadian rhythmicity during benzodiazepine discontinuation which is a serious stressor to the sleep-wake regulation system. Disruptions in circadian sleep-wake rhythmicity are common in patients with psychiatric and neurodegenerative disorders and are closely intertwined with the sleep abnormalities described above [68,78]. In schizophrenia, a link between disrupted rest-activity cycles and cognitive performance has been suggested [79].

The participants’ subjective evaluation of sleep quality was examined using the Pittsburgh Sleep Quality Index [80]. Studies have shown that subjective sleep quality is associated with quality of life and that objective sleep measures alone do not capture the individual experience of severity of subjectively perceived insomnia [81,82,83].

Sleep spindles are electrophysiological characteristics of stage 2 non-REM sleep (N2) and can be described as waxing and waning, 11 to 16 Hz, sleep oscillations, which are generated within the thalamus and relayed to the cortex via thalamo-cortical loops [84]. Several studies have found a profound sleep spindle deficit in patients with schizophrenia (both in medicated and in antipsychotic-naïve patients) as well as in healthy first-degree relatives, and sleep spindle deficit is considered a schizophrenia endophenotype candidate [85,86,87] (Figure 4). Recently, evidence has accumulated that sleep spindle deficits and cognitive impairments in schizophrenia are associated [88,89], but it is unclear how sleep spindle activity and morphology relate to specific cognitive abilities. Most previous studies considered simple motor tasks and not measures of more complex neurocognitive functioning. Therefore, we examined the association of cognitive functioning as measured using a neurocognitive test battery with sleep spindle characteristics in the schizophrenia subsample in the SMART baseline data set. In this paper, we only analysed patients with schizophrenia since the above described theories pertain specifically to schizophrenia.
Figure 4: A: EEG oscillations in different sleep stages. B: Sleep spindles are markedly reduced in patients with schizophrenia relative to healthy controls. *Figure and adapted legend reprinted from Ferrarelli and Tononi, Schizophrenia Research 2017;180:36-43.* Reprinted with permission from the publisher.

4.2 Methods and materials

4.2.1 Eligibility criteria

We included patients with a diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder, aged 18 years or above, and treated with a combination of antipsychotic drug and benzodiazepine for at least three months. We excluded fertile women not using safe contraceptives, pregnant or lactating women, and subjects with aggressive/violent behaviour, mental retardation, pervasive developmental disorder, dementia, epilepsy, terminal illness, severe somatic comorbidity, inability to understand Danish, hepatic impairment or allergy to compounds in the trial medication.
4.2.2 Benzodiazepine taper procedure and clinical assessments

Eighty-six patients with schizophrenia or bipolar affective disorder were randomized to either prolonged-release melatonin (2 mg) or identical placebo immediately before beginning guided gradual dose reduction of long-term benzodiazepine treatment. Participants were referred to the trial mainly from outpatient clinics but some participants were also referred during or right after hospitalization. The rate of benzodiazepine discontinuation was planned individually in agreement with each participant starting from a default regimen of 10-20% dose reduction every week or every second week depending on the starting dose. As dosage declined it was often necessary to increase the intervals or decrease the weekly or fortnightly percentage reduction. We interviewed and examined participants at baseline and every second month and contacted them by phone every week. Most participants visited the research clinic hosting the trial but some of the participants living in sheltered homes were not able to leave their environment and were therefore interviewed and examined, as far as the practical circumstances allowed, in their homes. Total trial duration was 24 weeks (6 months). Please see Table 2 for overview of clinical and technical examinations during the trial.

Method and reporting followed the guidelines laid down by CONSORT [90].

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>8 weeks</th>
<th>16 weeks</th>
<th>24 weeks</th>
</tr>
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<tbody>
<tr>
<td>Benzodiazepines (dose)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Co-medications</td>
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<td>X</td>
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<td>X</td>
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<td>Neurocognition (BACS)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Psychophysiology (not included in thesis)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Sleep assessment (PSG and actigraphy)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Psychopathology (PANSS)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Quality of life (WHO-5 and SWN-S)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Withdrawal symptoms (BWSQ-2)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Subjective sleep quality (PSQI)</td>
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<td></td>
<td>X</td>
</tr>
<tr>
<td>Social functioning (PSP)</td>
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</tr>
<tr>
<td>Sociodemographic characteristics</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

21
Plasma-level of benzodiazepines X
Adverse events X X X
UKU X X

Table 2: Collection of data.
BACS: Brief Assessment of Cognition in Schizophrenia (described below)
PSG: Polysomnography (described below)
PANSS: Positive and Negative Syndrome Scale is a rating scale for measuring symptom severity in schizophrenia [91]. It covers the last week, requires a 45-50 minutes interview and comprises items describing positive symptoms, negative symptoms and more general psychopathology.
WHO-5: WHO-5 Well-Being Scale is a generic scale on subjective well-being (an aspect of the quality of life concept) [92].
SWN-S: Subjective Well-being under Neuroleptic Treatment scale (short form) is a disease-specific scale on subjective well-being [93].
BWSQ-2: Benzodiazepine Withdrawal Symptom Questionnaire (described below).
PSQI: Pittsburgh Sleep Quality Index (described below).
PSP: Personal and Social Performance Scale is a scale on psychosocial functioning [94].
UKU: short version of the Udvalget for Kliniske Undersøgelser side effect rating scale [95] to assess if benzodiazepine discontinuation would be associated with changes in antipsychotic side effects (benzodiazepines are sometimes used for this purpose).

Adapted from Baandrup et al. BMC Psychiatry 2011, 11:160. Reprinted with permission from the publisher.

4.2.3 Outcomes

The primary outcome was benzodiazepine daily dosage at end of the trial (24 weeks follow-up). This was determined by self-report supported by prescribing information. For participants not completing the trial, the actual benzodiazepine daily dosage was drawn from up-to-date prescribing information securing 100% availability of the primary outcome measure. For participants reporting complete benzodiazepine cessation at follow-up up, a blood test controlling benzodiazepine plasma level was drawn.

Secondary outcomes included proportion of participants with complete benzodiazepine cessation, pattern of benzodiazepine dose over time, benzodiazepine withdrawal symptoms, subjective and objective sleep outcomes, neurocognition, psychophysiology (early information processing), social functioning, psychopathology, quality of life, and circadian rhythm parameters. The psychophysiological data are not included in this thesis.
Specific procedures and measures

Polysomnography: We used one-night polysomnography (PSG) to evaluate the objective sleep quality. PSG is the gold standard for assessing sleep continuity parameters and for evaluating the microstructure of sleep. PSG comprises electrophysiological recordings of brain activity, i.e. electroencephalography (EEG with frontal, central and occipital derivations), muscle activity, i.e. surface electromyography (EMG of the submentalis and anterior tibialis muscles), eye movements, i.e. vertical and horizontal electrooculography (EOG), nasal air flow, temperature of in- and exhaled air, pulse oximetry, respiratory inductance plethysmography (measuring the effort to breathe), and electrocardiography. The PSG equipment was mounted by a sleep technician in the afternoon, worn at home for the rest of the day and during the night and was removed by the patient the next morning. The PSG recordings were manually scored in 30 seconds epochs according to the American Academy of Sleep Medicine criteria [96]. See Figure 5 for illustration of PSG equipment and characteristics of sleep stages. Sleep spindle detection was performed using an automatic spindle detector previously validated; please refer to paper 6 for details. We evaluated spindle density (separating between fast and slow spindles) together with the following measures of spindle morphology: duration, oscillation frequency, peak-to-peak amplitude, and symmetry. The analyses were performed both for non-REM sleep and for N2 sleep only.

Pittsburgh Sleep Quality Index (PSQI): The PSQI is a self-report questionnaire which assesses the subjective sleep quality within the last month. The instrument consists of 19 items covering different aspect of sleep quality [80]. Each
item is scored on a 0-3 interval scale, yielding seven component scores that produce one composite score from 0-21 where higher scores represent worse sleep, and with a suggested cut-off between good and poor sleepers at a composite score of ≤5 for good quality sleep and >5 for poor quality sleep [97,80]. The instrument has been quite extensively validated in different study populations and shows strong reliability and validity [98].

**Actigraphy:** To evaluate the circadian sleep-wake pattern during benzodiazepine withdrawal and melatonin supplement we performed actigraphy for three consecutive days and nights at baseline and at 24 weeks follow-up. This outcome was not well described in the trial protocol (paper 1) because initially the actigraphy data were primarily meant to validate the PSG data. We have published a paper comparing PSG and actigraphy data [99] which is not included in the thesis. During the trial we decided to assess the actimetric data with regard to sleep-wake regulation since this is an integrated part of, and often difficult to distinguish from, sleep disturbances. The actigraphy measures kinetic energy during wrist movement for several consecutive days and nights and thus makes evaluation of the rest-activity cycle possible. The activity data were processed by standard software and displayed as an actigram (see Figure 6). We did not use standardized software derived measures of sleep continuity parameters (e.g. total sleep time, sleep latency) because they were by definition inferior to the simultaneously obtained PSG derived measures. Instead we used the raw activity data (activity counts/epoch using an epoch length of 30 sec) and calculated measures that better capture and describe certain elements of circadian rhythmicity comprising the interdaily stability (IS), the intradaily variability (IV) and the relative amplitude (RA). These measures were originally introduced into the field by Eus Van Someren and we used his proposed algorithms for the calculation [100]. The IS is a measure of the invariability between days, it will be 1 for perfect IS and thus high predictability of the 24 hour rest-activity pattern. The IV is a measure of the fragmentation of the rhythm, i.e. the frequency and extent of transitions between rest and activity. The RA is a measure of the extent of difference between activity counts during rest and activity, respectively [100].
Brief Assessment of Cognition in Schizophrenia (BACS): To evaluate cognitive functioning we used the BACS which is a neurocognitive test battery covering several cognitive domains that are profoundly impaired and correlated with prognosis in schizophrenia [101]. The BACS comprises six subtests assessing the following domains: verbal memory (list learning), working memory (digit sequencing), motor speed (token motor test), verbal fluency (category fluency and letter fluency), attention and processing speed (symbol coding), and executive function (the Tower of London test). The neurocognitive testing was performed by research staff that had been trained to administer and score the BACS.

The Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ-2) comprises 10 items referring to disturbances of perception and sensation, seven to somatic symptoms, and three independent: depressed mood, loss of control of voluntary movement, and memory loss [102]. These self-rated 20 items pertain to the preceding two weeks and are each scored on a 3-point scale (absent (0), moderate (1) or severe (2)) and are summed into a total score of maximum 40. The questionnaire has been validated to measure benzodiazepine withdrawal symptoms in a reliable way [103].

4.3 Results

4.3.1 Main results (paper 2)

Eighty-six participants were included in the trial. The flow through the trial is depicted in Figure 7.
We found that total daily benzodiazepine dosage decreased steadily in both intervention groups (N=42 in melatonin group; N=44 in placebo group) but there was no difference between groups in either total daily benzodiazepine dosage at end of the trial (as illustrated in Figure 8) or in proportion of participants with benzodiazepine cessation (38.1% (16/42) in melatonin groups versus 47.7% (21/44) in placebo group, p=0.32). Thus, temporary treatment with melatonin did not facilitate benzodiazepine tapering.
Figure 8: Estimated linear time course of the mean benzodiazepine daily dosage (in mg diazepam equivalents) in the melatonin group (blue line) and in the placebo group (green line). There was no statistically significant difference between the intervention groups. *Reprinted from Baandrup et al. The World Journal of Biological Psychiatry 2016; 17(7):514-24.* Reprinted with permission from the publisher.

Benzodiazepine withdrawal symptoms (BWSQ-2) did not increase during the trial and there was no difference between intervention groups. We observed no worsening of clinical symptoms or manifestations of the underlying psychiatric illness while the participants were tapered from benzodiazepine therapy. On the contrary, we found a significant decrease (i.e. improvement) in PANSS total score in the total sample from baseline (mean 63.48, SD 12.99) to follow-up (mean 60.70; SD 16.30) (p = 0.025), however, probably not of clinical relevance. We also found that discontinuation of benzodiazepines did not de mask antipsychotic side effects since antipsychotic side effects, as measured with a short version of the UKU, significantly improved from baseline to follow-up (p < 0.001).

4.3.2 Neurocognitive performance, subjective well-being and psychosocial functioning (paper 3)

Cognitive outcome data were available for N=40 in both groups at baseline, and at 24 weeks follow-up N=30 in the melatonin group and N=31 in the placebo group. Cognitive abilities improved statistically significantly during
benzodiazepine discontinuation; however, it was difficult to separate the effect of benzodiazepine discontinuation from practice effects because we did not include a control group of patients not withdrawing from benzodiazepines. When comparing the effect size (0.69 for the composite score) of the current cognitive improvement with previous studies examining similar study populations, we clearly found that this surmounted the effect size that could be expected due to practice effects in itself (0.45) [104,105]. Study participants did not return to levels of cognitive functioning comparable to the general population after benzodiazepine discontinuation, probably due to the inherent core of the schizophrenia illness that cognitive impairment constitutes in itself. Thus, there seemed to be a true reversal of the cognitive suppressing effects of chronic benzodiazepine use. The improvement in cognitive abilities as a function of time and thus of benzodiazepine dose reduction was evident for all BACS subscales except for motor speed. Melatonin per se did not have any cognitive improving efficacy. The results are illustrated in Table 2. All the BACS scores are given as z-scores. For more detailed information, please see paper 3.

<table>
<thead>
<tr>
<th>BACS</th>
<th>Main effect of intervention</th>
<th>Main effect of time</th>
<th>Intervention*time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>Numerator</td>
<td>p</td>
</tr>
<tr>
<td></td>
<td>df</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite</td>
<td>0.115</td>
<td>1</td>
<td>0.735</td>
</tr>
<tr>
<td>score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal</td>
<td>0.282</td>
<td>1</td>
<td>0.597</td>
</tr>
<tr>
<td>memory</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Digit</td>
<td>0.515</td>
<td>1</td>
<td>0.475</td>
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<td>sequencing</td>
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</tr>
<tr>
<td>Verbal</td>
<td>0.199</td>
<td>1</td>
<td>0.657</td>
</tr>
<tr>
<td>fluency</td>
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<tr>
<td>Token</td>
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<td>1</td>
<td>0.831</td>
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<td>motor</td>
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</tr>
<tr>
<td>Symbol</td>
<td>1.455</td>
<td>1</td>
<td>0.231</td>
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<tr>
<td>Tower</td>
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<td>0.976</td>
</tr>
<tr>
<td>of London</td>
<td></td>
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</tr>
</tbody>
</table>

Table 2 MMRM (mixed-model with repeated measures) analyses of BACS composite and sub scales (Type III fixed-effects). Statistically significant results at the p < 0.005 level is shown in bold. Reprinted from Baandrup et al. European Archives of Psychiatry and Clinical Neuroscience 2017;267(2):163-171. Reprinted with permission from the publisher.
We found that neither benzodiazepine withdrawal nor treatment group affected subjective well-being or psychosocial functioning.

4.3.3 Objective and subjective sleep quality (Paper 4)

PSG data were available for N=43 at baseline and N=23 at 24 weeks follow-up (N=10 in the melatonin group and N=13 in the placebo group). We confirmed a pathological sleep pattern in patients with severe mental illness: fragmented sleep with no or very little slow wave sleep (see example in Figure 9) which did not change significantly after benzodiazepine withdrawal. Melatonin did not improve sleep efficiency as hypothesized. Objectively assessed sleep continuation parameters (total sleep time, sleep latency, REM latency, time awake after sleep onset, number of awakenings) and sleep architectural parameters, i.e. the percentage of sleep spent in different sleep stages, were not associated with benzodiazepine tapering which thus did not induce or aggravate sleep disturbances in the participants. The only significant finding was a positive association of benzodiazepine dosage with amount of N2 sleep, i.e. lowering the benzodiazepine daily dosage was associated with increased N2 sleep thus reversing the benzodiazepine induced suppression of N2 sleep.

PSQI data were available for N=84 at baseline and N=55 at 24 weeks follow-up (N=28 in the melatonin group and N=27 in the placebo group). The subjective sleep quality as assessed by this standard questionnaire was significantly better in the melatonin group at 24 weeks follow-up compared with the placebo group. The mean PSQI global score was 5.21 in the melatonin group and 7.41 in the placebo group (P = 0.02). The PSQI global score improved from a mean of 8.18 (SD 4.43) to 5.21 (2.96) at follow-up in the melatonin group and thus almost reversed sleep quality from poor to good as evaluated using the PSQI cut-off value of 5. The PSQI global score also improved in the placebo group (and thus only attributable to benzodiazepine discontinuation) but to a lesser extent (from 8.23 (3.06) at baseline to 7.41 (3.87) at follow-up).
Figure 9: Hypnogram from trial participant with chronic schizophrenia presenting with highly irregular sleep cycles. Sleep latency: 1 hour 7 min; N2 sleep: 75%; Slow wave sleep (N3): 0%; Sleep efficiency: 60%; Total sleep time: 3 hours and 11 min.

4.3.4 Circadian rest-activity rhythms (paper 5)

Actigraphy data were available at baseline for N=48 participants (N=20 in the melatonin group and N=28 in the placebo group) and at follow-up for N=30 (N=11 in the melatonin group and N=19 in the placebo group). See Figure 10 for an example of outcome data. From these data, we calculated three measures IS, IV and RA (see above) describing the circadian rhythmicity and found no difference between intervention groups as regards the RA, and a trend significant difference in favour of the melatonin group as regards the IV. Finally, we found that the IS differed significantly between groups indicating more stable circadian sleep-wake regulation in the melatonin group compared with placebo at 24 weeks follow-up.
Figure 10: Example of an actigram from a trial participant with chronic schizophrenia 57 y, male, paranoid schizophrenia, 4 mg clonazepam:
Highly irregular rest-activity cycle, irregular periods of sleep, fragmented sleep. For comparison with actigram with healthier sleep-wake rhythm, please refer to Figure 3. The black bars indicate activity counts, the coloured lines are recorded light input and the light blue boxes indicate periods with probable sleep as derived from the software algorithm. The dark blue boxes are time excluded from analysis (before and after wearing the actigraph).

When comparing the total sample from baseline to follow-up, we found that activity counts had generally increased during all intervals along the day with only the first 6-hour interval after wake-up being close to statistical significance (p=0.063). See Table 3. This analysis included only patients with actigraphy data both at baseline and at follow-up (N=30).

<table>
<thead>
<tr>
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<th>Baseline</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>t</td>
</tr>
<tr>
<td>1-6 hrs after wake up time</td>
<td>52240±29594</td>
<td>65176±34731</td>
<td>-1.933</td>
</tr>
<tr>
<td>7-12 hrs after wake up time</td>
<td>59177±33083</td>
<td>74659±40067</td>
<td>-1.655</td>
</tr>
<tr>
<td>13-18 hrs after wake up time</td>
<td>35618±26546</td>
<td>42040±32144</td>
<td>-0.801</td>
</tr>
<tr>
<td>19-24 hrs after wake up time</td>
<td>8423±8817</td>
<td>12299±13271</td>
<td>-1.400</td>
</tr>
</tbody>
</table>

Table 3: Activity counts per six hours (mean ± SD), measured the second night and day in the whole sample (N=30).

4.3.5 Sleep spindle activity and morphology (paper 6)

Thirty-seven patients with schizophrenia medicated with both antipsychotics and benzodiazepines were evaluated with one night PSG. As expected, we found a sleep spindle deficit when comparing absolute values of sleep spindle density in our sample of schizophrenia patients with previous samples of healthy controls [106]. Using regression models with BACS composite and subscales as the dependent variable and sleep spindle density and sleep spindle morphology as independent variables, controlling for age, gender, total symptom score (PANSS total) and daily dose of benzodiazepines and antipsychotics, we did not find any conclusive pattern. The only statistically significant association after Bonferroni correction was between slow sleep spindle density frontally and motor speed.
4.4 Discussion

Foremost, it should be emphasized that this trial is concerned with long-term/chronic treatment with benzodiazepines. It is unquestionable that benzodiazepines have a first-line placement in the acute phase of many psychiatric illnesses including acute psychotic exacerbations in schizophrenia or manic episodes with pronounced insomnia in bipolar disorder. In such circumstances, benzodiazepines are among our most efficient and non-toxic drugs acutely relieving symptoms until the effect of antipsychotics or mood stabilizers set in. The national restrictions on benzodiazepine prescribing that resulted from our polypharmacy-mortality study [17] and successive similar studies should not be misinterpreted as arguing against benzodiazepines for acute psychiatric illness where induction of sufficient sleep and amelioration of distressing anxiety can be life-saving. It is when patients are caught in chronic benzodiazepine use that the results from the current randomized controlled trial are relevant. On the basis of this trial, we can assure our patients that benzodiazepine discontinuation will not lead to deterioration of sleep disturbances and will most likely improve cognitive functioning. The only cognitive subdomain that was not improved during benzodiazepine tapering was motor speed. This is in agreement with the literature indicating that chronic users develop tolerance to the impairment of motor performance that is observed after acute administration of benzodiazepines in non-users [7,57]. The largest improvement with time was observed for verbal learning which is in line with the literature indicating that verbal learning is one of the cognitive domains most profoundly impaired by chronic benzodiazepine use [57] and thus with a high potential for reversal when benzodiazepines are discontinued. Another contributing factor might be that the same verbal memory word list was used for each administration of the BACS (at that point in time only BACS version A was translated into and validated in Danish), and thus results from this subscale were probably more sensitive to re-test effect than the remaining subscales.

With the applied questionnaires we could not detect any changes in subjective well-being during benzodiazepine taper. Thus, an ability to think more clearly and reduced perceptions of being isolated in a bell, which the majority of the participants spontaneously reported, were not strong enough to manifest themselves in the applied patient-reported outcomes. However, it is a valuable message to patients worried about benzodiazepine withdrawal that their well-being is most likely not to change, and at least not deteriorate, as they gradually taper usual benzodiazepine treatment.

In patients with severe mental illness, sleep disturbances and/or circadian disruptions often pose a barrier for the motivation to pursue a goal of benzodiazepine discontinuation from both patients’ and caregivers’ point of view. The data from this trial comprise some evidence that it will be relevant to consider melatonin as add-on treatment during benzodiazepine discontinuation in patients with severe mental illness and sleep disturbances and/or circadian
disruptions, because melatonin seems to improve subjective sleep quality and circadian stability in this particular patient group.

Comparing actigraphy data from pre to post tapering, we found a general increase in activity. We interpret this as increased motor activity after benzodiazepine discontinuation/dose reduction and thus as a sign of reduced sedation and apathy (common benzodiazepine side effects). From these results in isolation, it is not possible to differentiate between reduced levels of sedation or, alternatively, withdrawal induced motor agitation or restlessness. However, bearing in mind the results from the BWSQ-2 with no indications of increased amount of withdrawal symptoms during the trial, we are rather certain that the observed increase in daytime activity was not due to distressing withdrawal symptoms. The results of the sleep spindle analyses must be seen in a broader context as a contribution to a growing field of research which will, eventually, lead us closer to a thorough understanding of exactly how sleep disturbances at different levels contribute to, and/or are related to, the different symptom domains in schizophrenia and in other disorders along the psychosis spectrum. If future research holds the promise that sleep spindles play an important role in the pathophysiology behind neurocognitive impairments, then the next step will be to develop medication that can increase sleep spindle density. Our finding of a relationship between slow sleep spindle density and motor speed was rather unexpected because hitherto fast spindles have shown the closest association with cognition [107].

Limitations to the conclusions that can be drawn from this trial include the attrition rate, and for sleep examinations a further reduction in sample size at both baseline and at follow-up because of an unwillingness to participate in and to repeat the sleep examinations which by some participants were found to be overwhelming and stigmatizing. Twelve subjects in each intervention group discontinued the trial but more subjects refused to repeat the sleep examinations which markedly reduced the sample for sleep evaluation at follow-up. Consequently, sleep and circadian results from follow-up must be interpreted with some caution and the lack of difference between the melatonin and the placebo group might be due to a type II error. Regarding the primary outcomes on benzodiazepine dose and cessation, we had complete data also for the dropouts and therefore these results can be regarded as highly valid. The mixture of patients with schizophrenia and bipolar disorder might be seen as limiting the external validity of the results and thus jeopardizing the generalizability. However, the research community has been encouraged by US authorities (the National Institute of Mental Health) to move away from diagnosis-specific research and move towards transdiagnostic research to get a better understanding of symptom domains (e.g. sleep disturbances and arousal-rest dysfunction) [108]. Within this concept, a lack of diagnosis-related generalizability must be accepted.
5 Cochrane Review: Pharmacological interventions for benzodiazepine withdrawal (papers 7-8)

5.1 Introduction

Benzodiazepines remain to be one of the most prescribed pharmaceutical drug classes worldwide [109]. Benzodiazepines are efficient pharmaceutical agents in the acute treatment of severe anxiety, agitation and insomnia but are not recommended for long-term treatment due to development of tolerance, physical and psychological dependence together with other serious side effects as summarized above. The clinical challenge is how to prevent efficient short-term use to continue into long-term use where efficacy is largely unestablished and the range of side effects together with a risk of abuse constitute a major clinical and public concern [109]. Since people are often maintained on benzodiazepine treatment despite recommendations of the opposite, there was a need for a Cochrane review on pharmacological methods to facilitate benzodiazepine discontinuation. The way such an intervention might work is to reduce or ameliorate benzodiazepine withdrawal symptoms thus rendering the subjects capable of finishing the gradual withdrawal at a higher pace and minimizing the risk of benzodiazepine relapse.

Another way a pharmacological intervention might work is to reduce symptoms of anxiety or insomnia that occur as part of a rebound phenomenon or when being de masked as usual benzodiazepine dosage is decreased.

5.2 Methods and materials

This systematic review was conducted according to the standards of the Cochrane Collaboration which included exact definitions of all aspects of the methods as published in the review protocol (paper 7). Briefly, we included all randomized controlled trials investigating the efficacy of a pharmaceutical agent to facilitate benzodiazepine discontinuation in users who were dependent on benzodiazepines and/or had used benzodiazepines on a daily basis for at least two months. All kinds of pharmacological interventions were included, and we only pooled pharmacologically similar agents avoiding broader groups of heterogeneous compounds such as ‘antidepressants’ or ‘anticonvulsants’. All included trials were assessed with the Cochrane Risk-of-bias tool and the results and the quality of the evidence was integrated using the standardized GRADE approach [110,111,112].

34
5.3 Results

Thirty-eight randomized controlled trials were included in the review but data for the meta-analysis could only be extracted from 35 trials due to poor reporting. Many different interventions were studied and no single intervention was examined in more than four trials. We evaluated 18 different comparisons including a total of 2295 subjects. From single trials there were indications of a beneficial effect of valproate (regarding benzodiazepine discontinuation and benzodiazepine relapse), tricyclic antidepressants (benzodiazepine discontinuation and withdrawal symptoms), pregabalin (benzodiazepine withdrawal symptoms and anxiety), captodiame (benzodiazepine withdrawal symptoms and anxiety), carbamazepine (anxiety), flumazenil (withdrawal symptoms and anxiety), and cyamemazine (benzodiazepine relapse). Using evidence from two trials, paroxetine seemed to have a beneficial effect regarding benzodiazepine withdrawal symptoms, but this effect did not last until longest follow-up. Furthermore, paroxetine reduced anxiety. It was not possible to systematically extract data on adverse events because they were insufficiently reported. Overall, the results were heterogeneous and inconsistent, sample sizes were small, the quality of the evidence assessed using the GRADE approach was low or very low, and many studies were involved with the pharmaceutical industry. An example of a forest plot for the melatonin versus placebo comparison is shown in Figure 11.

![Figure 11: Example of forest plot for the melatonin versus placebo comparison: benzodiazepine discontinuation at end of intervention.](image)

5.4 Discussion

The results from this review comprise an important updated contribution to the evidence gathered in total on this topic. We conclude that a number of different pharmacological interventions have been investigated but mostly in underpowered studies of low scientific quality. Most results were based on single small-sized randomized trials with a high risk of type II error. Consequently, it was not possible to translate the findings of the review into any meaningful
clinical recommendation, except that treatment with additional medication during benzodiazepine taper cannot generally be recommended. It would certainly strengthen the field if the scientific community could unite the efforts and focus on the most promising agents and testing these in larger and well conducted trials if we ever are to gain more thorough and reliable information on how to facilitate benzodiazepine withdrawal. Another way forward, as inspired from the results from the SMART trial, would be to focus on more narrow study populations when evaluating the efficacy of specific pharmaceutical agents to facilitate benzodiazepine withdrawal, and to choose the experimental intervention based on a more detailed understanding of the biological mechanism of action. For example, physical withdrawal symptoms are thought to emerge from an imbalance between glutamatergic and GABA-ergic activity with relative glutamatergic excess due to downregulation of the GABA-ergic system as response to long-term benzodiazepine treatment. Thus, drugs potentiating the GABA-ergic system and inhibiting the glutamatergic system would be potential candidates to success when discontinuing benzodiazepines. Pregabalin and gabapentin bind to voltage-gated calcium channels modulating the synthesis of GABA and glutamate [113] and might thus be effective in reducing physical benzodiazepine withdrawal symptoms. In the current review, pregabalin was examined in one trial examining 106 participants with generalized anxiety disorder reporting reductions in withdrawal symptoms and anxiety with pregabalin [114]. However, these beneficial effects did not transform into increased success regarding actual benzodiazepine discontinuation. Gabapentin was evaluated in one small trial (N=19) of methadone maintenance users [115]. We could not extract data from this trial but the authors reported no difference between intervention groups on any of the reported outcomes. Thus, pregabalin seems to possess a promising potential for facilitating benzodiazepine withdrawal and merits further investigation. The lack of efficacy regarding benzodiazepine discontinuation might be due to insufficient sample size since the trial sequential analysis showed that the required information size was not met.

On the contrary, the theoretical underpinnings for using e.g. lithium for benzodiazepine discontinuation seem less convincing. Efficacy regarding withdrawal symptoms does not, however, guarantee benzodiazepine cessation because the psychological equivalent, craving, might not be ameliorated by the same neurobiological mechanisms. The perception of craving is thought to involve complex circuitry involving prefrontal cortex, amygdala and hippocampus [116]. Specific anti-craving drugs have been developed for alcohol dependence targeting opioid receptors in the reward circuitry (naltrexone, nalmefene) and targeting specific glutamatergic NMDA-receptors (acamprosate) but these drugs have not been tested for benzodiazepine dependence.

The previous Cochrane review on this topic covered the literature until October 2004, included eight trials involving 458 participants, and focused on benzodiazepine dependence in outpatient settings [117]. The authors concluded that
carbamazepine might facilitate gradual benzodiazepine discontinuation due to a modest benefit in reducing withdrawal symptoms. Another previous meta-analysis, including both inpatient and outpatient settings, found imipramine in combination with guided discontinuation programs more effective than guided discontinuation alone [118]. These conclusions are not supported by the current review. Another systematic review focusing on general practice and outpatient settings did not find that substitutive pharmacotherapies were of any help in benzodiazepine discontinuation[119] and thus very much in line with what we found. Psychological interventions were found to be superior to gradual dose reduction in some of the cited reviews [119,118]. Psychosocial interventions have been further analysed in a recent Cochrane review [120], which concluded that cognitive behavioural therapy in combination with gradual taper is somewhat superior to benzodiazepine taper alone but that the effect is not sustained beyond three months follow-up. Results from single studies suggested a beneficial effect of a tailored letter from the general practitioner versus a generic letter from the general practitioner, a standardized interview versus treatment as usual, and relaxation techniques versus treatment as usual. Overall, the evidence base for recommending specific psychosocial interventions to facilitate benzodiazepine discontinuation is just as meagre as for the pharmacological interventions.

Attitudes and beliefs towards benzodiazepines have long been subject to controversy in the literature and amongst clinicians. As Lader dramatically describes it: “Almost from their introduction the benzodiazepines have been controversial, with polarized opinions, advocates pointing out their efficacy, tolerability and patient acceptability, opponents depreciating their adverse effects, dependence and abuse liability” [109]. We cannot for certain predict in which users benzodiazepine prescribing will become chronic, but the rate of transition from short-term to long-term use depends on the patient population. Two recent French studies investigating trajectories of benzodiazepine treatment in new users have found that for use of hypnotic benzodiazepines there is a prevalence of 40% of occasional use and 60% of regular use whereas for anxiolytic benzodiazepines the numbers are 60% for occasional use, 10% for early increasing use, 17% for late increasing use and 13% for increasing followed by decreasing use [121,122]. These numbers seem to underpin a higher risk of more permanent use and perhaps addiction for hypnotic versus anxiolytic benzodiazepines. A study from Japan found that among new benzodiazepine users 35.8% continued for three months, 15.2% continued for one year, and 4.9% continued for eight years. They found the following predictors for long-term use: older age, psychiatrist-prescriber, regular use, high dose, and concomitant prescription of other psychotropic drugs [123]. It is a consistent finding that the highest benzodiazepine prescribing rates are found in the elderly which is quite alarming considering the substantially increased risk of side effects in this population. It is remarkable that this public concern
has not attracted more attention from national authorities or from advocates in the scientific literature arguing that restrictions on benzodiazepine use have come too far.

To summarize current clinical recommendations for benzodiazepine discontinuation: Due to the risk of severe withdrawal reactions including withdrawal delirium in users who have developed tolerance and dependence, benzodiazepines should be gradually withdrawn when treatment has continued for more than a few weeks. This is supported by results from two reviews finding improved outcomes for gradual dose reduction compared with usual care [117,119]. However, the studies included in these reviews applied a tapering regimen that was either not very well described or faster (20-25% dose reduction per week) than usually applied in clinical practice. Consequently, it is not possible from the literature to give advice on the ideal tapering rate, but there is currently no evidence that very slow tapering (i.e. ongoing for years) are associated with higher success rates. Likewise, there is no compelling evidence to support current national recommendations that short-acting benzodiazepines should be substituted with long-acting ones before gradual discontinuation (https://www.sst.dk/da/udgivelser/2008/benzodiazepin_nedtrapningsskemaer_til_praktiserende_laege_r#Skema 15). Such a strategy might theoretically be associated with a smoother withdrawal course but evidence for its efficacy in clinical practice is lacking [117].
6 Observational studies: Different aspects of antipsychotic prescribing using register data

6.1 Antipsychotic polypharmacy and health service costs (paper 9)

6.1.1 Introduction

The prevalence of antipsychotic polypharmacy has been approximately 20% for the last four decades with variations between regions, being higher in Asia and Europe than North America [124]. Antipsychotic polypharmacy prescribing rates have increased in North America, decreased in Asia and fluctuated in Europe [124] despite the fact that international treatment guidelines discourage the use of antipsychotic polypharmacy, except for patients with schizophrenia not sufficiently responding to clozapine. Specifically in Denmark, an increase in cross-sectional prevalence of antipsychotic polypharmacy was observed from 17.2% in 1996 to 30.8% in 2006, and after that a decrease to 24.6% in 2012 [125]. As previously described, antipsychotic polypharmacy is associated with increased frequency of side effects, drug-drug interactions, medication errors and reduced compliance, and there is no evidence to support a superior efficacy compared with antipsychotic monotherapy. Very few studies exist that examine the derived costs of antipsychotic polypharmacy finding that polypharmacy is associated with significant increases in costs of care compared with monotherapy [126].

6.1.2 Methods and materials

We evaluated a sample of 736 outpatients with a schizophrenia spectrum diagnosis who were divided into two groups according to a cross sectional evaluation of treatment with either antipsychotic polypharmacy or antipsychotic monotherapy. We analysed the total costs of primary and secondary health service use controlling for age, gender, disease duration, psychiatric inpatient admissions and treatment site. Costs on antipsychotic medication use were not included in the analyses because medication costs are responsible for only a minor fraction of the total societal costs of schizophrenia treatment [127]. We did not include indirect costs (lost productivity) and intangible costs (pain and suffering). Data on resource utilization and costs were extracted from central Danish registers for a period of two years (2007 and 2008). We analysed the total direct costs for health care services for each year examining the association with antipsychotic polypharmacy. Data on psychosocial functioning (Global Assessment of Functioning, GAF-F, from the split GAF scale) were available for a subset of the sample and this was included as a covariate in a subgroup analysis.
6.1.3 Results

We found that antipsychotic polypharmacy was associated with significantly increased health care costs compared with antipsychotic monotherapy. Total health care costs were 17% to 25% higher in the antipsychotic polypharmacy compared with the antipsychotic monotherapy group. The excess costs were in particular driven by increased consumption of mental health care services, which in absolute numbers amounted to 7-9 excess bed days and 6-9 excess outpatient contacts per year for patients prescribed antipsychotic polypharmacy compared with antipsychotic monotherapy. The subgroup analysis indicated that part of the excess costs were attributable to decreased level of psychosocial functioning.

6.1.4 Discussion

The findings of increased cost of health care services, in particular mental health care services, associated with antipsychotic polypharmacy could be explained by complications to the polypharmacy regimen including drug-drug interactions, side effects and lack of adherence. Such factors in combination might lead to increased need of outpatient services and psychiatric hospitalizations. However, due to the observational design of the study it is not possible to infer any causal relations. As suggested by the subgroup analysis, it is highly possible that at least some of the observed excess health service costs were attributable to reduced psychosocial functioning of the patients receiving antipsychotic polypharmacy making this medication status a marker of illness severity/poor psychosocial functioning and not a causal factor driving these patients’ increased use of health care inpatient and outpatient services. Still, the study has a stronger design than many previous cost studies which collected data on health service utilization from patient questionnaires or telephone interviews. The literature in this area is scarce and mainly concerned with costs of medication not taking into account the much higher budget post of other mental health care costs. Valluck et al. performed a retrospective cohort study using Medicaid claims data from more than 55000 subjects treated with antipsychotics and found that antipsychotic polypharmacy was associated with higher medication costs also when adjusting for case mix (age, gender, ethnicity, mental disorders, hospitalization, index antipsychotic and concomitant antipsychotic drugs) [128]. A naturalistic US study following patients for one year after the initial prescribing of an antipsychotic and only including medication costs found that antipsychotic polypharmacy added substantial incremental costs compared with monotherapy [129]. In this study, the probability of having an antipsychotic added to the initial antipsychotic medication depended on which antipsychotic compound was prescribed initially and for some compounds resulted in
more than 100% incremental costs [129]. Thus, health economic evaluations of various antipsychotic compounds should not focus narrowly on drug expenses but also on the typical subsequent prescribing regimen. Future studies should aim at collecting simultaneous data on antipsychotic prescribing and important confounders including illness severity and level of psychosocial functioning. In a US study of patients with treatment resistant schizophrenia using data from the Medicaid database it was reported that monotherapy with clozapine was associated with reduced disease-specific and all-cause health care costs compared with antipsychotic polypharmacy [130], probably reflecting superior therapeutic efficiency of clozapine.

6.2 Characteristics and prognosis of incident antipsychotic users (papers 10-11)

6.2.1 Introduction

The use of antipsychotic medications is steadily increasing in Denmark as well as in many other societies [131,132,133,134], partly due to a growing number of licensed uses, but also due to a rising trend of off-label prescriptions [131]. This must be considered a societal concern due to potentially severe adverse events. In papers 10 and 11 we aimed to characterize incident users of antipsychotics with regard to prescribing practices and possible consequences in terms of mental health care costs and occupational capabilities. A better understanding of the characteristics of these new users of antipsychotics might aid in directing future interventions to optimize antipsychotic prescribing practices.

6.2.2 Methods and materials

These studies were register-based linking the following Danish nationwide registers: the Central Psychiatric Research Register, the Register of Medicinal Product Statistics, and Statistics Denmark. We identified all adult incident users of antipsychotics defined as filling of at least one antipsychotic prescription within the study period from 2007 to 2012. Subjects who had collected at least one prescription for an antipsychotic compound up to three years before were not considered as new users and thus excluded. Three sets of analyses were performed 1) descriptive analyses of prescribing patterns the first year after the index prescription, 2) regression analyses of association of different antipsychotic combination prescribing practices with use of mental health care services, and 3) regression analyses of association of antipsychotic prescribing patterns with labour market affiliation, duration of welfare payments (i.e.
unemployment benefits, disability pension, and other social security benefits), and increment in gross income. Regression analyses were adjusted for age, gender, diagnosis, marital status, education, mental health care contacts and various interaction terms.

Antipsychotic medication use was analysed in intervals of 60 days based on a pre-analysis of the typical length of antipsychotic prescriptions which we found to be approximately one month (30 days). This 60 days’ interval was chosen to ensure that most subjects would fill at least one antipsychotic prescription during an interval and at the same time the interval should be sufficiently short to detect prescribing changes. For each new antipsychotic user we categorized the prescribing pattern the following year, divided into 60 days periods, as follows: continued monotherapy, switched antipsychotic, discontinued antipsychotic, or combined (with another antipsychotic, with an antidepressant or with a benzodiazepine).

6.2.3 Results

During the study period, 154351 adult subjects initiated treatment with antipsychotics. We found that more than half (54%) of incident antipsychotic users had their initial prescription issued in the primary care sector and thus were not registered with a diagnosis in the Central Psychiatric Research Register. The other half (46%) of the subjects, i.e. those who had presented with sufficiently severe symptoms to be referred to or to seek secondary mental health care services, was available for further description and analyses. For this subset of the sample (71254 subjects), the index antipsychotic prescription was most often issued in relation to a diagnosis of adjustment reaction or unipolar mood disorder, was mostly of very short duration (45% discontinued treatment within the first four months) and most often consisted of quetiapine or chlorprothixene. In most diagnostic groups there was a majority of women being prescribed antipsychotics, especially in recurrent depressive disorder and personality disorders where approximately 70% of the study population were women. The mean age was below 50 years except for organic mental disorders, in particular Alzheimer’s dementia where the mean age of new antipsychotic users was close to 80 years.
Figure 12: Schematic presentation of antipsychotic prescribing patterns the first year after the initial antipsychotic prescription. Other = combination treatment antipsychotic-antipsychotic, antipsychotic-antidepressant, or antipsychotic-benzodiazepine. See text for further explanation.

Figure 12 illustrates the prescribing patterns in 60 days intervals across the first year after the initial antipsychotic prescription. The figure shows that there was a steady rate of switch to another antipsychotic compound than the initial one during the first year of around 10% each 60 days interval. Many (45%) of the incident users of antipsychotics discontinued the medication within the first four months after the initial prescription, and after the first year 59% had stopped the medication. Combining the antipsychotic with an antidepressant was common initially (47%) but then almost halved (to 21%) after the first year. Combining the antipsychotic with a benzodiazepine occurred in 20% of cases but diminished to 9% after the first year. Antipsychotic polypharmacy was prescribed for less than 5% and did not change much during the first year.

When repeating the descriptive analyses for individual diagnostic categories the results revealed the following important points: for schizophrenia, the incidence of antipsychotic polypharmacy was 14% initially, and 11% after the first year. For patients with unipolar mood disorder, 70% were prescribed an antidepressant and 20-25% a benzodiazepine in addition to the antipsychotic compound.
Figure 13: Time to first hospitalization according to antipsychotic drug regimen (Cox regression analysis). 1: antipsychotic–antidepressant combination; 2: antipsychotic–benzodiazepine combination; 3: antipsychotic–antidepressant–benzodiazepine combination; 4: antipsychotic polypharmacy.

*Figure reprinted from Baandrup et al. Soc Psychiatry Psychiatr Epidemiol 51(4):505-12.* Reprinted with permission from the publisher.

The regression analysis in paper 10 demonstrated that antipsychotic polypharmacy and antipsychotic-benzodiazepine co-treatment was associated with increased use of mental health care services defined as hospitalizations and visits to outpatient clinics and emergency rooms. Furthermore, antipsychotic polypharmacy was associated with increased risk of psychiatric hospitalization compared with other antipsychotic combination regimens (Figure 13).

According to the regression models in paper 11, we found that both antipsychotic polypharmacy and antipsychotic–antidepressant combination treatment was associated with increased duration of well-fare payments/social security benefits, and that antipsychotic polypharmacy and antipsychotic-benzodiazepine combination was associated with leaving the labour market significantly earlier. Gross income increment was not associated with antipsychotic prescribing regimen. However, the explanatory power of these regression models was low.
6.2.4 Discussion

The results clearly show that incident antipsychotic users constitute a heterogeneous group and that transient off-label prescribing seems to prevail, especially in combination with an antidepressant. Considering the lack of evidence of therapeutic benefit in off-label conditions this is clearly a worrying prescribing pattern due to the potentially serious side effect profile of most antipsychotics, which will, in most cases, lead to an unfavourable risk-benefit ratio. Quetiapine and chlorprothixene were most often prescribed indicating that the majority of initial antipsychotic prescriptions had an unspecific sedative purpose.

We corroborated our own findings from the health economic study (study 9) regarding the association between antipsychotic polypharmacy and mental health service utilization. Variation in the investigated occupational outcome measures are most likely multifactorial and not sufficiently explained by the limited set of variables that we were able to adjust for in the study.

The most important limitation regarding the interpretations of the results from these studies is the lack of measure of disease severity and other psychosocial factors influencing use of mental health care services and occupational outcome measures. We applied a rough proxy of disease severity but obviously this left us with a substantial amount of residual confounding. We must expect that subjects treated with antipsychotic polypharmacy share by definition a more unfavourable course of illness and hold fewer occupational resources. What can be suggested from these results is that antipsychotic treatment, especially in combination with another antipsychotic or in combination with a benzodiazepine, could serve as a marker for subjects who are in risk of becoming marginalized and thus are in need for extended support to maintain occupational abilities. What can also be inferred from these data is that antipsychotic polypharmacy regimens were not able to neutralize the inherent poor prognosis of this patient group and thus did not contribute to recovery.

The results are in agreement with the international literature on off-label antipsychotic prescribing where a recent review found that many off-label prescribing practices reflect temporary treatment for mild symptoms indicating a safety problem due to the heavy side effect profile of many antipsychotics [135]. Marston et al. conducted a study in UK primary care of subjects prescribed antipsychotics [136], which roughly corresponds to the half of our subjects that were not recorded in the National Patient Register and thus were not included in our analyses. The UK study identified more than 47000 individuals who were prescribed antipsychotics within a primary care setting. In accordance with our study, off-label prescribing was identified as conditions other than psychosis and bipolar disorder. For subjects treated with first-generation antipsychotics more than 50% were for off-label conditions and for second-generation
antipsychotics this number varied between 38% and 64%, being particularly high for quetiapine. Extrapolating the UK results to Denmark, we cannot expect rates of off-label antipsychotic prescribing in primary health care to be lower than in the current analysed sample of subjects treated within secondary mental health care. The UK study found higher antipsychotic prescribing rates in females and older people above 80 years of age. This is similar to the tendencies in our study population and calls for continuous attention on optimizing antipsychotic prescribing habits.

Tsang et al. conducted a systematic review of predictors of vocational outcome among individuals with schizophrenia and found that cognitive functioning was by far the most important predictor of future occupational functioning [137]. Additional significant predictors included education, negative symptoms, social support and skills, age, and previous history of successful employment. Thus, future studies aiming to evaluate cost-effectiveness of antipsychotic prescribing practices should aim to include these predictors, in particular cognitive functioning, which will only be possible in a clinical trial setting because cognitive measures are not available in current nationwide registries.

The studies presented here make it possible to differentiate better the raw numbers of increasing antipsychotic use and thus provide a basis for academia and/or regulatory authorities to take action on the transient and unnecessary use of antipsychotics putting non-psychotic individuals at risk of severe side effects when their current situation might as well have been handled purely behaviourally.
7 General discussion

The overall aims of this thesis were to investigate pharmaceutical agents to facilitate benzodiazepine withdrawal in long-term benzodiazepine users, to investigate the feasibility and safety of discontinuing long-term benzodiazepine use in patients with severe mental illness, and to investigate if the increasing societal use of antipsychotics, including polypharmacy, is justified in terms of diagnosis and prognosis.

The main value of the results lies in providing documentation for a markedly favourable outcome when tapering benzodiazepines in subjects with severe mental illness. The thesis adds a substantial amount of knowledge about benzodiazepine tapering after chronic use in patients with severe mental illness. We show that it is, indeed, possible to taper chronic use of benzodiazepines within this patient population without inducing measurable withdrawal symptoms, deterioration in psychosocial functioning, or clinical instability. Sleep continuity is not affected by benzodiazepine discontinuation; on the contrary, there is indication that benzodiazepine induced suppression of N2 sleep is reversible upon withdrawal. Benzodiazepine tapering is associated with improved functioning in several cognitive domains to a degree not solely explicable by re-test effects. Melatonin does not in general facilitate benzodiazepine tapering but our data suggest that it might, during benzodiazepine withdrawal, be a relevant temporary supplement for patients with circadian rhythm disruptions or poor subjective sleep quality. Apart from this, it is not possible to recommend pharmacological agents to facilitate benzodiazepine tapering due to a fragmented and insufficient evidence base.

In Denmark, restrictions laid down by the national authorities have led to a decrease in benzodiazepine prescriptions during the last decades. In particular, there has been a decrease in long-term and high dose users [138,139]. Examples of these restrictions include an obligation to issue a benzodiazepine withdrawal schedule when patients are discharged from hospital; general practitioners (who prescribe the vast majority of benzodiazepines) are not allowed to renew benzodiazepine prescriptions by phone, instead patients must show up for a personal consultation; benzodiazepine treatment must be restricted to two weeks for insomnia and to four weeks for anxiety [140].

In the US, there has been a marked increase of 67% in benzodiazepine prescribing from 1996 to 2013 and a documented increase in number of deaths involving benzodiazepines from 1135 in 1995 to 8791 in 2015. Consequently, concerns have been raised of insufficient knowledge of prescribers regarding the addictive potential and, when ingested daily, the risk of worsening anxiety and insomnia and causing death [141]. The issue of increased risk of death associated with benzodiazepine use is not isolated to combined antipsychotic-benzodiazepine prescribing but has been found in a number of other settings as well [142,143,144]. The results of these studies showing increased risk of death associated
with hypnotic drugs have been difficult to interpret due to methodological limitations including lack of adequate confounder control. A French cohort study investigating the association between hypnotic drugs and mortality in 6700 elderly subjects found increased mortality hazard ratios with hypnotic drug use when analysing the raw data, but these findings disappeared when adjusting for sociodemographic and lifestyle variables and chronic disease including sleep and psychiatric disorders [145]. The authors concluded that the underlying psychiatric disorders were the principal confounders of the observed association. However, this does not rule out that benzodiazepines in combination with other central nervous system depressants may be a significant contributor to increased risk of death. In the US, there is a specific concern because opioids are almost always involved in benzodiazepine-related death, and there is increasing concern of an ‘opioid epidemic’ [146,147,148]. In the light of these international data and observations, the current results and data from the SMART trial must be considered highly relevant and clinically useful.

Identifying profound sleep disturbances and poor sleep quality both before and after benzodiazepine withdrawal, this thesis also touches upon the question of how to best treat chronic insomnia in schizophrenia and other severe mental illnesses. There is now evidence to recommend CBT-i (cognitive behavioural therapy, specifically focusing on insomnia) for insomnia comorbid with psychiatric and medical conditions: two recent meta-analyses found moderate to large effect sizes with greater improvements in psychiatric than in medical populations [149,150]. No studies examining patients with schizophrenia or bipolar disorder were included in the meta-analyses, but a randomized controlled pilot trial of CBT-i in patients with schizophrenia with persisting psychotic symptoms has shown reductions in insomnia with large effect size [151]. Another pilot randomized controlled trial investigating CBT-i in interepisode bipolar disorder type I patients found that the intervention was effective in reducing risk of mood episode relapse and in improving sleep and functioning [152]. An important and obvious problem is the practical feasibility of such a recommendation due to very limited access to CBT-i both in primary and in secondary mental health care. To solve this, a large randomized trial has been conducted using an internet-delivered version of CBT-i with improvement in sleep measures with large effect sizes lasting one year after the intervention [153]. Psychiatric comorbidity was allowed but efficacy and safety issues in patients with severe mental illness remain to be verified in future studies.

This thesis adds knowledge on health economic aspects in relation to antipsychotic combination treatment which is a research area with scarce knowledge. Most studies in this area are cost-of-illness studies evaluating total societal costs of schizophrenia often in comparison with other disorders or conditions. The most recent of these international collaborative studies, covering the cost of brain disorders in Europe, concluded that schizophrenia is still among the most expensive mental illnesses, also when excluding indirect costs [154]. This study reported that 60% of the total
costs of brain disorders (i.e. mental and neurological disorders) are due to direct costs (37% direct health care costs and 23% direct non-medical costs) and 40% are due to indirect costs (loss of productivity). A report from the Danish National Board of Health from 2015 analysed societal costs of a number of somatic and psychiatric disorders and concluded that schizophrenia is associated with the highest direct costs to treatment and care of all diseases included in the analysis thus exceeding conditions such as diabetes and stroke [155]. The excessive costs were illustrated by the fact that schizophrenia was attributable to one third of all psychiatric hospitalisations and outpatient contacts [155]. The report found that 14% of total costs of schizophrenia is due to medication costs which is markedly higher than previously reported in the literature [127]. This might be due to higher medication costs now than previously, where cheaper first-generation antipsychotic agents were mostly used, and some of the difference might also be due to methodological differences between the report and previous studies. Cost-effectiveness studies, i.e. studies evaluating costs of treatment in relation to the effect, are very scarce. In the few studies that exist, the focus have been on long-acting injectable antipsychotics (LAI) compared with oral antipsychotic treatment. The LAIs are often (at least for the second generation agents) quite expensive compared with the oral formulations, but a review of cost-effectiveness studies concluded that LAIs are probably cost-saving due to reduced rate of hospitalizations and relapse compared with oral administration [156]. It was noted, however, that most of the included studies were dominated by evaluations of risperidone LAI, most of evaluations excluded indirect costs of schizophrenia, and studies were difficult to compare across countries due to methodological differences [156]. Recently, two population-based register studies were published by Tiihonen et al. confirming that LAIs are associated with a markedly (around 20%) lower risk of rehospitalisation than their corresponding oral formulation [157,158].

What can be concluded from the population-based register studies of prescribing practices in incident antipsychotic users? It is evident that off-label prescribing practice is quite common and that antipsychotics from the onset of treatment are often prescribed together with a benzodiazepine or an antidepressant (de novo polypharmacy). Thus, it is clear that general prescribing practice does not adhere very strictly to standard prescribing guidelines advocating primarily monotherapy. Off-line prescribing is undoubtedly necessary in selected clinical cases but the data document a widespread and frequent use of de novo combination treatment that goes way beyond ‘selected cases’. Thus, a considerable number of subjects are exposed not only to the currently documented side effects of antipsychotics and other psychotropics but also to side effects that we might not yet be fully aware of. The latter includes a possible risk of volume reduction of certain brain regions including prefrontal cortex and temporal lobes which has been found in longitudinal studies of medicated patients with schizophrenia [159]. However, in these studies it has not been possible
to differentiate between the effects of the illness and the effects of medication, and similar brain structural abnormalities have been found in drug-naïve patients with schizophrenia [159]. These data are accumulated from years of clinical schizophrenia research and no comparable imaging data exist for people treated with antipsychotics for off-label conditions.

The way to improve prescribing practices must lend evidence from behavioural science which is a topic too broad to be covered here. Many initiatives have already been implemented and specifically in schizophrenia the quality of the treatment is being monitored by the Danish Schizophrenia Registry [160,161]. This database covers all inpatients and outpatients enrolled in secondary mental health care with a schizophrenia diagnosis. Unfortunately, during the last couple of years the validity of the data have been compromised by insufficient registration due to a lack of support from top managements and due to IT-solutions with poor compatibility with requirements for data registration. The overarching benefit of a database monitoring the quality of schizophrenia treatment transnationally is the possibility of comparing different regions/departments/hospitals and thus be aware if someone is moving out of range on one or more of the defined quality indicators. It is also possible to be inspired and learn from e.g. specific departments that score high on one or more specific indicators. Thus, a national database for monitoring and improving the quality of the treatment has a range of advantages compared with more local initiatives which are typically short-term and with no set-up to register and maintain data.

8 Future directions

How do we treat chronic insomnia in severe mental illness if not with benzodiazepines or off-label antipsychotics? This is a massive clinical challenge since many patients struggle with sleep disturbances causing a substantial degree of instability in their daily lives. A better treatment of sleep disturbances could prevent many relapses and re-hospitalizations [151,152]. Interventions to improve sleep disturbances and circadian disruptions in severe mental illness should be based on current knowledge of shared neurobiological abnormalities behind sleep disturbances and clinical symptoms. One ongoing initiative is a US randomized trial investigating the efficacy of a therapeutic program (based on CBT-i) treating sleep disturbances in patients with severe mental illness, and outcome is evaluated both clinically (using actigraphs) and from the patient perspective using patient reported outcome measures specifically developed to assess subjectively perceived sleep disturbance and sleep related functional impairment [162,163]. Other suggestions of future transdiagnostic interventions to improve sleep and stabilise sleep-wake regulation include:
therapeutic modulation of light therapy, social rhythm therapy (social interaction is an important zeitgeber for circadian rhythmicity), and anxiety focused interventions (because anxiety-related arousal interferes with sleep) [73].

What is the perspective of development of future anxiolytic and hypnotic agents? Several GABA A-receptor agonists selective for the α2 subunit have been developed. Such compounds would be expected to have anxiolytic action, but be devoid of sedation and addictive potential because these effects are associated with the α1 subunit. None of these drugs has as yet been approved for clinical use [164]. An interesting hypnotic drug development area is the orexin receptor. Orexins (also known as hypocretins) are neuropeptides that stimulate wake-promoting systems in the complex regulation of sleep and wake [165]. An orexin receptor antagonist (Suvorexant) has been approved in the US and Japan. Data from trials including only subjects with primary insomnia (i.e. not insomnia associated with any psychiatric or medical condition) shows that it reduces sleep onset latency with between 5 and 13 minutes and increases total sleep time with around 20 minutes compared with placebo [165]. More experience with this drug in clinical practice is needed to gain more knowledge on effect, tolerability and safety in different patient populations.

What about melatonin? Which place in treatment of chronic insomnia should melatonin hold? Prolonged-release melatonin has a licensed indication for use in subjects > 55 years of age with primary insomnia showing a small-moderate effect on sleep quality and morning alertness [166,167]. There is some evidence for use of melatonin for insomnia related to disruptions of circadian sleep-wake rhythm as in delayed sleep phase syndrome [168,169], autism spectrum disorders [170,171] and ADHD (evidence most convincing for childhood ADHD [172]). For primary insomnia, a recent meta-analysis found evidence of effect of melatonin on sleep onset latency but with limited clinical relevance (mean reduction in sleep onset latency 5.05 minutes, 95% CI -8.51 to -1.59) and 3 out of 5 randomized controlled trials only included subjects above 55 years of age [173]. Thus, for primary insomnia in younger subjects the evidence is very scarce. The latest review of melatonin in secondary insomnia, i.e. insomnia comorbid with psychiatric or medical conditions (now called comorbid insomnia), was published in 2006 and found no effect of melatonin [174], but some evidence for melatonin as sleep aid for specific diagnostic categories as described above has appeared since. When focusing specifically on schizophrenia, two small-sized randomized trails examining melatonin as augmenting drug to treat insomnia in patients with schizophrenia have been published. Shamir et al. examined 19 patients with schizophrenia in a randomized placebo-controlled cross-over design (melatonin 10 mg, 6 weeks) reporting improvement in actigraphy measured sleep efficiency with melatonin but only in a subsample of poor sleepers [175]. Suresh Kumar et al. investigated treatment with melatonin (3-12 mg) versus placebo (N=20 in each group) for 15 days in stable patients with schizophrenia and found that melatonin improved questionnaire derived measures of sleep
including quality and depth of sleep, night time awakenings and duration of sleep [176]. Thus, larger well-conducted trials using both subjective and objective sleep outcome measures are needed to evaluate the potential role of melatonin to ameliorate sleep disturbances in schizophrenia. Other possible indications for melatonin in schizophrenia that need further investigation include treatment of antipsychotic side effects where a recent review found no effect of melatonin to treat tardive dyskinesia [177], but several studies have indicated a potential benefit in attenuating adverse metabolic side effects associated with certain second generation antipsychotics [178,179].
**Dansk resumé**

Denne afhandlings overordnede formål var at undersøge, hvordan længerevarende behandling med benzodiazepiner bedst udtrappes, hvordan sådan en udtrappingsproces forløber hos patienter med alvorlig psykiske lidelse, samt om den øgede brug af antipsykotika, herunder polyfarmaci, i befolkningen generelt synes at være berettiget i forhold til diagnose og prognose.


Der var tale om en reel forbedring, også når man tog re-test effekten i betragtning, hvilket bedst forklares som en revertering af den benzodiazepin-inducerede kognitive forringelse. Tæthed og morfologi af søvnspindler (elektrofysiologiske karakteristika under non-REM søvn) kan tolkes som et udtryk for funktionaliteten af thalamo-kortikale forbindelse og har en betydning i forhold til kognition. Der var imidlertid ikke nogen klar sammenhæng mellem tæthed og morfologi af søvnspindler og kognitivt funktionsniveau hos medicinerede patienter med skizofreni. Dette kan muligvis for klares af kompleksiteten af det anvendte neurokognitive testbatteri.

I Cochrane review’et præsenteres en omfattende gennemgang og analyse af alle til dato afprøvede lægemidler i forhold til at facilitere nedtrapning af benzodiazepiner hos langtidsbrugere. Review’et omfattede 38 randomiserede forsøg, men
grundet ringe rapportering var det kun muligt at ekstrahere data fra 35 forsøg, der undersøgte 18 forskellige sammenligninger hos i alt 2295 forsøgsdeltagere. Baseret på enkeltstående forsøg fandtes mulige terapeutiske effekter af valproat (med hensyn til benzodiazepin ophør og benzodiazepin relapse), tricykliske antidepressiva (benzodiazepin ophør og seponeringssymptomer), pregabalin (benzodiazepin seponeringssymptomer og angst), captodiamin (benzodiazepin seponeringssymptomer og angst), carbamazepin (angst), flumazenil (seponeringssymptomer og angst) og cyanemazin (benzodiazepin relapse). For paroxetin var der evidens fra to studier for en gavnlig effekt med hensyn til benzodiazepin seponeringssymptomer, men denne effekt varede ikke ved til længste opfølgningstidspunkt. Samlet set var resultaterne inkonsistente, bivirkningerne utilstrækkeligt rapporterede, og den underliggende evidens af for ringe kvalitet til at retfærdiggøre kliniske anbefalinger.

Det sundhedsøkonomiske studie viste, at antipsykotisk polyfarmaci ikke var omkostningseffektivt i forhold til antipsykotisk monoterapi, idet effekten betragtes som sammenlignelig, men antipsykotisk polyfarmaci var associeret med større omkostninger grundet et øget forbrug af sundhedsydelser. Denne association var formentlig i nogen grad influeret af utilstrækkelig confounder kontrol, hvilket blev bekræftet af en subgruppe analyse, hvor sammenhengen mellem antipsykotisk polyfarmaci og sundhedsøkonomiske omkostninger varforklaret af psykosocialt funktionsniveau. De registerbaserede epidemiologiske studier demonstrerer, at kortvarig off-label antipsykotisk behandling udgør en forholdsmaessig stor del af stigningen i forbrug af antipsykotiske lægemidler, som er konstateret i Danmark i løbet af de seneste årtier. Således udgør individer med alvorlig psykisk lidelse kun en mindre del af nye brugere af antipsykotika.

Forskellige former for antipsykotisk kombinationsbehandling, især antipsykotisk polyfarmaci, fandtes at være associeret med øget brug af sundhedsvæsenets ydelser inkl. reduceret varighed til psykiatrisk indlæggelse såvel som kortvarig tilknytning til arbejdsmarkedet og lange perioder på overførselsindkomst. Resultaterne var justeret for sygdommens sværhedsgrad, idet vi brugte et proxy mål (tyngde af forbrugte sundhedsydelser), men må alligevel betragtes som værende forbundet med en betydelig risiko for rest confounding som tydeliggjort af de statistiske modellers lave forklaringsgrad. Fremtidige studier bør inkludere øvrige betydende variable, herunder et eller flere mål for den kognitive funktion, for bedre at kunne beskrive det komplekse netværk af associationer mellem formentlig multiple betydende variable. En vigtig implikation af fundene er, at de belyser det faktum, at behandling med antipsykotisk polyfarmaci på ingen måde synes at kunne neutralisere den iboende dårlige prognose for disse patienter og således ikke bidrager til recovery.

For at kunne reducere uhensigtsmæssig brug af psykofarmaka har vi brug for bedre behandlingsmuligheder og en bedre implementering af nationale monitoreringstiltag sigtende mod at øge kvaliteten af klinisk behandling og pleje.
English summary

The overall aims of this thesis were to investigate pharmaceutical agents to facilitate benzodiazepine withdrawal, to investigate the feasibility and safety of discontinuing long-term benzodiazepine use in patients with severe mental illness, and to investigate if the increasing societal use of antipsychotics, including polypharmacy, is justified in terms of diagnosis and prognosis.

The SMART trial investigated potential therapeutic benefits of temporarily adding melatonin to subjects diagnosed with schizophrenia or bipolar disorder during gradual and guided tapering of usual benzodiazepine treatment. Eighty-six subjects in combined treatment with antipsychotics and benzodiazepines were randomized to a fixed dose of prolonged-release melatonin versus placebo. All subjects were closely monitored during the tapering process and most of them managed to comply with the tapering regimen, but there was no difference between the groups in benzodiazepine dosage or proportion of participants with benzodiazepine cessation at 24 weeks follow-up. Benzodiazepine withdrawal symptoms, subjective well-being and psychosocial functioning did not change significantly from pre to post taper or between groups. We found no sign of rebound insomnia or other deteriorating effects on sleep continuity or sleep architecture when comparing objective sleep evaluations (polysomnography data) pre and post taper, and there was no difference between groups. Melatonin improved circadian rhythm stability (as measured with actigraphy) and subjective sleep quality after benzodiazepine discontinuation. Thus, melatonin cannot be recommended to facilitate benzodiazepine discontinuation in general, but based on the results from the SMART trial could be considered to aid benzodiazepine tapering in individuals with severe mental illness and disrupted circadian rhythmicity and/or impaired subjective sleep quality. Likewise important is the finding that neurocognitive functioning improved when benzodiazepines were tapered. This improvement was evident even when taking the re-test effect into consideration and was best explained by at least partly reversal of benzodiazepine induced cognitive dysfunction. Sleep spindles, a characteristic electrophysiological manifestation of functionality in thalamo-cortical circuits in non-REM sleep, were not found to be clearly associated with neurocognitive functioning in medicated patients with schizophrenia, but this might have been explained by the complexity of the applied neurocognitive measures.

The Cochrane review presents a thorough description and analysis of all evaluated pharmacological agents to facilitate benzodiazepine discontinuation after long-term use. The review included 38 randomized clinical trials but due to poor reporting it was only possible to extract data from 35 trials examining 18 different comparisons and including a total of 2295 subjects. Based on single trials, there were indications of a beneficial effect of valproate (benzodiazepine
discontinuation and benzodiazepine relapse), tricyclic antidepressants (benzodiazepine discontinuation and withdrawal symptoms), pregabalin (benzodiazepine withdrawal symptoms and anxiety), captodiame (benzodiazepine withdrawal symptoms and anxiety), carbamazepine (anxiety), flumazenil (withdrawal symptoms and anxiety), and cyamemazine (benzodiazepine relapse). Using evidence from two trials, paroxetine seemed to have a beneficial effect regarding benzodiazepine withdrawal symptoms, but this effect did not last until longest follow-up. Overall, results were inconsistent, adverse events were insufficiently reported, and the quality of the evidence too poor to suggest any clinical recommendations.

Results from the health economic study showed that antipsychotic polypharmacy is also from an economic point of view an undesirable treatment modality because patients treated with antipsychotic polypharmacy generally consume more mental health care services than patients prescribed antipsychotic monotherapy. Thus antipsychotic polypharmacy cannot be considered cost-effective compared with monotherapy applying the evidence-based assumption that antipsychotic polypharmacy is no more effective than antipsychotic monotherapy. The association between antipsychotic polypharmacy and increased costs might have been to some extent caused by residual confounding because it was not possible to adjust for all potential confounders. This residual confounding issue was supported by a subgroup analysis finding that the association between antipsychotic polypharmacy and costs was explained by variation in psychosocial functioning.

The register-based epidemiological studies demonstrated that transient off-label antipsychotic prescribing contributed markedly to the increased use of antipsychotic treatment observed in Denmark during recent decades. Thus, subjects with severe mental illness comprised only a minor part of incident antipsychotic users. Different regimens of antipsychotic co-prescribing, in particular antipsychotic polypharmacy, were associated with increased use of mental health care services including reduced time to psychiatric hospitalization as well as short duration of labour market affiliation and long periods in need of welfare payments such as unemployment benefits and disability pension. These results were adjusted for illness severity using a proxy measure (severity of consumed mental health care services) but must be regarded as prone to residual confounding emphasized by a low explanatory power of the statistical models. Future studies should include other possible confounders such as cognitive functioning to better grasp this complex network of associations between multiple important variables. Furthermore, the findings shed light on the fact that antipsychotic polypharmacy regimens were not able to neutralize the inherent poor prognosis of this patient group and thus did not contribute to recovery.
To reduce the amount of inappropriate psychotropic prescribing we need better treatment options and better adherence to national monitoring programs aiming to improve the quality of clinical treatment and care.
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