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van Dijk, F.A.

Publication date
2019

Document Version
Final published version

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ISBN: 978-94-638-0467-7

Layout and design: Marten Dashorst
Financial support for printing this thesis was provided by University of Amsterdam
Printed by: proefschrifmaken.nl

Sense in subjectivity
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ACADEMISCH PROEFSCHRIFT
ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus
prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Aula der Universiteit
op woensdag 25 september 2019, te 13.00 uur

door

Floor Anna van Dijk
geboren te Utrecht

promotiecommissie

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CHAPTER 1

GENERAL INTRODUCTION

Schizophrenia and antipsychotics

Schizophrenia is a severe and disabling mental illness that has a major impact on social life, family relationships and the capacity to work (see Box 1.). It affects 0.7% of the Dutch population[1] and 0.3 – 1.0% of the population worldwide[2]. The course of the disorder is often chronic although the outcome for an individual is unpredictable. Schizophrenia takes place 5 (for males) and 6 (for females) in the global ranking list of disorders with most years lived with disability[3].

The cornerstone in biological treatment of schizophrenia and related psychotic disorders is antipsychotic medication. Pharmacological treatment causes (moderate) improvement or remission of psychotic symptoms but fails to substantially improve negative or depressive symptoms[4]. All antipsychotic agents may cause side effects. Antipsychotic agents can be distinguished by their affinity and selectivity for the dopamine D_2-receptor. The first generation of antipsychotics acts selectively on this receptor. Excessive D_2-receptor blockade can cause movement disorders, such as parkinsonism, akathisia or dystonia. Blockage of the D_2-receptor is also associated with reduced sense of motivation and a diminished emotional experience of natural rewards[5–7]. Newer antipsychotics have serotonergic, histaminergic and muscarinic binding potential, causing a different range of side effects. Serotonergic and histaminergic effects are associated with weight gain and sleepiness. Muscarinic effects are associated with constipation, a blurred vision and hypersalivation. Moreover, patients treated with antipsychotic medication have an elevated risk of developing cardiovascular comorbidity, diabetes, dyslipidaemia and hypertension. Besides impact on morbidity and mortality side effects may contribute to a vulnerability for functional impairments, in social relations and in self-esteem.

Box 1. Schizophrenia and related psychotic disorders

People suffering from schizophrenia may experience psychotic episodes, negative symptoms and a decline in cognitive functioning. Schizophrenia is a disorder with a heterogeneous symptom presentation and a heterogeneous course. Psychosis is characterized by a varying combination of delusions, hallucinations and disorganized thinking or bizarre behaviour. Patients with schizophrenia may also show negative symptoms: a loss of emotional expression, apathy, loss of initiative and poverty of speech and thinking. People with schizophrenia may withdraw from social interaction and sometimes show reduced self-care. Deficits in cognitive functioning that may occur are slow information processing and/or more effort needed to retrieve information. The related schizophreniform or schizoaffective disorder are mainly distinguishable from schizophrenia by the duration of symptoms or the occurrence of substantial mood disturbances. Schizophrenia affects 1.42 times more men than women[69]. Psychosis often emerges in late adolescence or early adulthood, with a peak between ages 18 and 25[70]. Predicting long-term outcome after first psychotic symptoms have emerged, remains difficult.

The patient's perspective, shared decision and subjective well-being

Since the introduction of antipsychotic agents, patients have prematurely stopped taking their medication. The most important and amendable predictor of antipsychotic medication adherence is the quality of the therapeutic relationship[8]. A personal approach focusing on the prevention or immediate treatment of adverse effects may improve medication adherence[9]. Patients with schizophrenia appreciate being involved in decisions about medical treatment. It improves treatment progress and outcome[9]. Patients prioritize information that can support them in making treatment decisions according to their individual needs and preferences[10,11].

To actively involve patients in treatment decisions, they need to be informed on the objective, evidence based treatment options. Moreover, this information needs to be weighted against patients' individual preferences.

The first antipsychotic agent chlorpromazine was introduced in the 1950s. Shortly after, experiments with healthy participants showed that apart from the overt motor symptoms, subtle emotional disturbances occurred during treatment with antipsychotic agents. They were described as a change in mood and internal drive and were not considered a part of negative symptoms[12,13]. This became known as 'the initial dysphoric response' to antipsychotic agents. The experiences of dysphoria and anhedonia were also reported by patients in periods that they did not meet the criteria for a depressive disorder[12]. The finding that this 'initial dysphoric response' predicted a poor treatment response[14,15], motivated research into the subjective experience of receiving antipsychotic treatment. The subjective response to (antipsychotic) treatment is important for the quality of life of patients[12] and is increasingly seen as an independent outcome measure that is especially relevant for treatment adherence and recovery[16–20].

Many factors influence the subjective experience of people with psychotic disorders, ranging from depressive symptoms to the opinion they have about their medication[18]. 'Subjective well-being under neuroleptic treatment' has been the most widely studied concept. It has been defined by De Haan et al. (2002) as "the subjective experience: aspects of mental or physical state, which patients report regardless of etiological attributions"[11].

The majority of patients with schizophrenia (63 – 95%) is able to complete self-rating scales reliably and consistently[18], even in a florid psychotic state[18,21].

Physicians and researchers on the contrary cannot make reliable judgements about patients' subjective well-being[18,22–24]. It is hence of major importance to consult patients directly on their subjective state.

The patient's perspective is important, because only patients can describe their situation in a relevant way. The improvement of the subjective experience related to antipsychotic treatment is a major therapeutic goal. Without acknowledging the patient's perspective, collaboration with the patient and compliance with therapy are difficult to achieve.

Box 2. Antipsychotic treatment

Psychotic symptoms are treated with antipsychotic medication. Psychotic symptoms (such as hallucinations or delusions) are associated with excessive dopaminergic neurotransmission in the striatum and the mesolimbic system[39]. Antipsychotic medication occupies the dopamine D_2-receptor, resulting in a reduction of dopaminergic neurotransmission and a gradual decrease in positive symptoms in most patients[39]. Often, mood disturbances and cognitive disturbances occur together with psychotic symptoms. Meta- and network analyses of randomized controlled trials have summarized differences between antipsychotic agents and their effects on positive, negative and cognitive symptoms and associated adverse effects[4,71]. This knowledge can be used to compare the advantages and disadvantages of individual antipsychotic agents.

Measurement of subjective well-being

The instrument most widely used in research on the subjective experience of schizophrenia patients is the Subjective Well-Being under Neuroleptic Treatment scale[12,18]. The currently used 20-item version (SWN-K) consists of 10 positive and 10 negative items. The score ranges from 20 (poor) to 120 (excellent). The scale can be filled in quickly (5 to 10 minutes) and consists of five subscales: emotional regulation, self control, mental functioning, social integration and physical functioning[25]. The SWN is translated into more than 40 languages and has been used in randomized double blind controlled trials and other studies[18].

The SWN-20 is sensitive for differences in dosage and type of neuroleptic treatment[18]. However, the association between the severity of psychopathology and subjective well-being is rather low: less than 16% of the variance of any SWN subscale could be explained by any of the PANSS subscales (the Positive and Negative Syndrome Scale, a common instrument to measure the severity of symptom dimensions of psychosis)[25]. Negative symptoms correlate stronger with subjective well-being scores than positive symptoms[25,26]. So, a substantial part of

the low scores cannot solely be explained by antipsychotic treatment and severity of psychopathology, which means subjective well-being should be seen as an independent outcome measure. The SWN-20 has been proven to be a reliable measure of subjective well-being also in relatives of patients with schizophrenia and healthy controls. These findings on the applicability of the SWN-20 indicate it's usefulness to measure subjective well-being.

The impact of a low subjective well-being

Subjective well-being in patients with schizophrenia is poorer compared to the general population and to other patients with severe psychiatric illnesses. One cohort study found that, despite similar severity of psychopathology, the average SWN scores for schizophrenia were lower (57.7) than those for schizoaffective disorder (64.1) or bipolar disorder (79.5)[27].

Poor subjective well-being under antipsychotic treatment is an additional risk for medication nonadherence[24,28]. After discontinuing antipsychotic medication, the risk of a relapse of psychotic symptoms is up to 80%[29]; therefore, enhancing subjective well-being of patients using antipsychotics may play a crucial role in the long-term management of the disorder. Also, early improvement of subjective well-being has been found to be predictive of long-term symptomatic remission in first episode schizophrenia patients, whereas early improvement in severity of symptoms was not[30].

The long-term effects of low subjective well-being are understudied. In one cohort study it was found that one in five patients persistently experiences low subjective well-being in the three years after treatment of a psychotic episode. Thirty percent of the patients with persistently low subjective well-being showed no or only minimal improvement in symptoms and functioning[16,31].

Scope of this thesis

The aims of the studies described in this thesis are twofold: first to describe the development of a tool designed to support patients in their decision for a specific antipsychotic agent; and second to increase the understanding of factors related to subjective well-being (e.g. antipsychotic medication, personality traits

or coping styles) in patients with a psychotic disorder and their siblings, in order to identify possible targets for intervention. Below, I will describe the main questions of the consecutive chapters.

Chapter I: How can we engage patients in choosing antipsychotic medication?

Up to 55 % of patients suffering from a first psychotic episode do not adhere to medication use in the first 4 years of treatment[32]. Treatment non-adherence is associated with an increase in relapse, suicide and hospitalization[33]. A good collaboration between patient and caregiver enables shared decision making. To actively involve patients in treatment decisions, online platforms can offer an accessible tool. Electronic decision support systems have demonstrated to improve patients' knowledge and as such can improve the quality of decision-making[34], Moreover, having a psychotic disorder does not prevent patients to be capable and willing to use internet applications[35–37].

Currently, patients in the Netherlands lack an accessible and valid information source to select antipsychotic medication from the perspective of their individual treatment needs. One platforms exists, called the 'MedicaWiki' initiative, yet it contains jargon (e.g. patients need to know terms like 'akathisia' instead of 'restlessness') and presents no clear overview of effects and side effects per agent. The British alternative 'Choice and Medication' provides evidence tables of many antipsychotics, but patients still have to weigh the information themselves. A platform is needed that assists patients to select the antipsychotic agent that best fits their needs and preferences, integrating current evidence on effectiveness and side effects, with a general aim to empower patients to be an active partner in shared decision-making.

We reviewed the scientific literature on the effects and side effects of antipsychotic medication and built a tool for ranking antipsychotic agents on their effectivity and tolerability that is open for the input of future studies. In this tool patient priorities and preferences are used to produce an individual ranking order of available antipsychotic drugs.

Chapter II: Is the D_2-receptor affinity of antipsychotic agents associated with subjective well-being in a naturalistic cohort study?

Neuroimaging studies have shown that a D_2-receptor occupancy of 60–70% is optimal in reducing psychotic symptoms as well as preserving subjective well-being of patients with recent-onset schizophrenia[6,7,38]. An explanation for this balance, is that processes of motivation and emotional experience as a con-

sequence of natural rewards are related to endogenous dopaminergic activity[39]. Also, the relationship between subjective well-being and D_2-receptor binding is not linear: a lower D_2-occupancy by antipsychotic agents is associated with a lower effectiveness on psychotic symptoms and results in a feeling of being overwhelmed (which is experienced as unpleasant), whereas higher D_2-receptor occupancy causes less reward from stimuli, resulting in flattened emotions[38].

Antipsychotic agents differ in their affinity for the dopamine D_2-receptor, as indicated by the Ki-value[40]. Antipsychotics with D_2-receptor affinity similar to dopamine (1.5 nmol/l) bind tightly to the D_2-receptor (e.g. haloperidol or risperidone), whereas antipsychotics with lower D_2-receptor affinity than dopamine (e.g. clozapine (148 nmol/l) and quetiapine (437 nmol/l)) bind more loosely than dopamine and allow higher levels of endogenous dopaminergic transmission[40].

In comparing subjective well-being during treatment with different antipsychotic agents, some second generation antipsychotics have shown to result in more positive emotional experiences[41] and subjective well-being[42] while occupying a similar level of D_2-receptors. This has been shown for olanzapine in comparison to risperidone and haloperidol[41] and for aripiprazole, after switching from olanzapine, risperidone or clozapine[42]. It is hypothesized that the partial agonistic action of aripiprazole preserves dopaminergic neurotransmission[42]. In contrast, three studies did not show differences in subjective well-being between antipsychotic agents[43–45] with the same level of D_2-receptor occupancy. Cross-sectional studies failed to show differences in subjective well-being[18].

These inconsistent results require further exploration. Our primary aim is to explore the relation between the estimated dopamine D_2-receptor affinity and subjective well-being in a large sample of patients with psychotic disorders using different antipsychotic agents. We hypothesize that patients using antipsychotics with lower D_2-receptor affinity as well as partial agonistic binding agents will report higher levels of subjective well-being compared to those using a tighter binding antipsychotic agents. Subsequently, we hypothesize that the subjective well-being of patients who switched to 'looser' binding agents will show more improvement over time compared to patients who switched to 'tighter' binding antipsychotics.

Chapter III: Can we use the SWN-20 as a global measure of momentary affective states in the last week?

From studies in the general population[46], it is suggested that positive and negative affective states are an underlying mechanism of subjective well-being. Momentary positive affective states are thought to enable a person to build up personal and social resources, so that it is easier to strengthen supportive relationships and increase subjective well-being[47]. A commonly used method to assess momentary affective states is the Experience Sampling Method, in which people register their mood ten times a day via an electronic device. However, this is a time-consuming procedure and presumes a substantial level of commitment of subjects. The SWN-20 is a retrospective, far less time-consuming tool, which could make it less necessary to measure momentary affective states. We hypothesize that momentary affective states measured by the ESM-method correlate highly with scores on the SWN-20. If proven, this would add an argument for using the SWN-20 as a global measure of momentary affective states in the last week.

Chapter IV: Are personality traits related to subjective well-being and do they influence the course of well-being over 3-6 years?

A good subjective well-being is associated with better health and longevity in the general population[48].

One study by Lambert et al. has investigated subjective well-being in patients with a psychotic disorder longitudinally and it shows that 20% of the patients has had an enduring low subjective well-being over three years[16]. Thirty percent of these patients showed no or minimal improvement in symptoms and functioning. A limitation in the study of Lambert et al. is that they did not include the influence of personality traits of participants in their evaluation. Personality traits such as neuroticism and extraversion have been shown to be associated with various quality of life measures in patients with a psychotic disorder[49–51]. So far, several studies have cross-sectionally assessed personality traits and their effect on subjective experiences in patients with schizophrenia[51]. These are often measured with the WHO Quality of Life-questionnaire[51], of which the psychological domain overlaps conceptually with the SWN-20[52]. As trait factors, neuroticism (high) and extraversion (low) have been found to correlate with reduced quality of life. As it is postulated that trait factors contribute stronger to quality of life than state factors[53], it would be of importance to investigate whether these personality traits are related to subjective well-being and its course over time. Additionally, we would be the first to map subjective well-being trajectories over a 6-year time period. If personality traits such as neuroticism predict a trajectory

of low subjective well-being, this would provide a clinical reference point for patients at risk of a persistent low well-being and subsequent risk for impaired social functioning and probably a high risk for symptom relapse.

Chapter V: Is coping with negative life events related to subjective well-being in patients and their healthy siblings?

The behavioural and cognitive efforts to prevent, alleviate or manage stress, are referred to as coping styles[54]. The capacity to adapt to life events on a cognitive and affective level is associated with the level of subjective well-being in the general population[55]. Additionally, Diener[55] suggests that subjective well-being is related to having an internal locus of control[56], meaning being able to attribute outcome to oneself instead of to external causes[46]. Significant interactions between locus of control and coping styles have been reported. Parkes[57] showed that individuals with internal attribution reported more adaptive coping strategies than those with external locus of control. In clinical research, coping is often conceptualized as a mediator between a stressor and clinical, or functional outcome measures. Patients with psychotic disorders deal with different types of stressors, including psychopathological symptoms[58–61] as well as everyday life events[62–64]. No studies exist that have assessed coping styles in patients with a psychotic disorder in relation to subjective well-being. Yet some evidence suggests that (subjective) quality of life measures are related to coping strategies in this population[65–68]. Taken together, these studies conclude that active and problem focused strategies seem to positively influence well-being. Emotion oriented and passive strategies have shown to negatively affect well-being. Symptoms and side effects of medication can render patients more passive than healthy subjects. Therefore we have included first-degree relatives to serve as a potential replication of above-mentioned findings in subjects with a liability for psychosis, but without illness related possible confounding effects such as functional impairment or medication effects. We hypothesized that active and problem focused coping strategies are positively associated and that passive and avoidant strategies are negatively associated with subjective well-being in both patients and their healthy siblings. Secondly, we explored whether coping styles mediate the relation between negative life events and subjective well-being in these groups.

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CHAPTER 2

Introduction: We present an online decision aid to involve patients with a psychotic disorder in shared decision making concerning the selection of antipsychotic medication.
Method: Patients selected effectiveness and adverse effects criteria from the Subject's Response to Antipsychotics-34 questionnaire. Numerical data from meta-analyses, clinical trial data, receptor affinities and expert opinions were used to rank antipsychotics on each criterion. When using the tool, patients indicate on a 5-point Likert scale how they value each (adverse) effect. The Likert scale values are combined in an algorithm with the rank orders of antipsychotics to create a personalized ranking.
Results: Criteria used were: effectiveness concerning psychotic, depressive and cognitive symptoms, weight gain, sexual dysfunction, drowsiness, hypersomnia, extrapyramidal symptoms, anticholinergic adverse effects, hypersalivation, nausea, dizziness, energy loss, blunted affect/less need for companionship. High level evidence was available for ranking weight gain, sexual dysfunction, menstrual disorders, extrapyramidal symptoms and effectiveness on psychotic symptoms. We used lower level evidence ranking the remaining criteria.
Discussion: A transparent procedure has resulted in an updateable tool to produce individual ranking of antipsychotics based on the patients' input.

THE PERSONAL ANTIPSYCHOTIC CHOICE INDEX – INTRODUCING A TOOL FOR SHARED DECISION-MAKING IN SELECTING ANTIPSYCHOTIC MEDICATION

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IN: PHARMACOPSYCHIATRY, 51 (2018), 89-99

Introduction

Adherence to medication remains a challenge in schizophrenia care. Up to 55% of the patients suffering from a first psychotic episode do not adhere to medication in the first four years after treatment[1]. Not using antipsychotic medication is associated with more severe psychotic symptoms and more frequent relapses[2]. Even partial non-adherence has substantial negative effects on course and outcome of schizophrenia[3]. Because of the heterogeneity of factors related to non-adherence, individually tailored approaches are needed to promote better medication adherence[2].

The most important modifiable factor to improve antipsychotic medication adherence is the quality of the therapeutic relationship[4]. A personal approach focusing on the prevention or immediate treatment of adverse effects may also improve medication adherence[5].

Research has shown that patients with schizophrenia appreciate being involved in decisions about medical treatment. It improves treatment progress and outcome[5]. Patients prioritize information that can support them in making treatment decisions according to their individual needs and preferences[6,7]. To actively involve patients in treatment decisions, web-based platforms can be an accessible intermediary. Electronic decision support systems have demonstrated to improve patients knowledge and as such can improve the quality of decision making[8], Moreover, patients with psychotic disorders are able and willing to work with internet applications[9–11].

Currently, patients lack valid information sources about antipsychotic medication from the perspective of their individual treatment needs. We therefore developed the 'Personal Antipsychotics Choice Index' (PACindex), an online smart decision aid for the selection of antipsychotic medication for patients with a primary psychotic disorder who are indicated for long term treatment. The application can be used at the start of treatment or for switching to another agent. It assists patients to select the antipsychotic agent that best fits their needs, integrating current evidence on effectiveness and side effects, with a general aim to improve the shared decision making process in clinical practice.

We will describe the development of the algorithm and online tool, demonstrating how the 15 most frequently prescribed antipsychotics in the Netherlands can be ranked based on several criteria concerning effectiveness and adverse effects.

2. Methods

2.1 Selecting criteria for effective and tolerable antipsychotic medication

Twelve patients with a first psychotic episode from the department of the Early Psychosis at the Academical Medical Centre of Amsterdam and four representatives of Dutch patients association Anoiksis formed a patient panel. The panel formulated a list of criteria concerning relevant effects and adverse effects based on the Subjects' Response to Antipsychotics questionnaire (SRA-34)[12].

2.2. Ranking antipsychotic medication on selection criteria

2.2.1. Selection of antipsychotic medication

We selected the 13 most-frequently prescribed antipsychotics in The Netherlands between 2006-2010, according to prescription data of the database of the Drug Information System of the Netherlands National Health Care Institute (Geneesmiddelen Informatie Project): quetiapine, risperidone, olanzapine, haloperidol, clozapine, pipamperone, aripiprazole, zuclopentixol, pimozide, penfluridol, sulpiride, flupentixol and perphenazine. In addition, we included lurasidone, entering the Dutch market in 2015, and amisulpride, anticipating its release in the Netherlands. Amisulpride is currently under research, being the first treatment option in the OPTiMiSE trial[13].

2.2.2. Literature search and level of evidence

Per criterion (intended effect or adverse effect), we searched PubMed and the Cochrane Database for meta-analyses, systematic reviews, clinical trials and case reports. Search terms were 'antipsychotics' 'antipsychotic medication' 'side effects' 'weight gain' 'sexual' 'sleep' 'sleepiness' 'drowsiness' 'extrapyramidal side effect' 'motor effects' 'secondary negative symptoms' 'anticholinergic effects' 'hypersalivation' 'nausea' 'dizziness' 'vertigo' 'creativity' 'affect' 'menstrual disorder' 'psychotic symptoms' 'positive symptoms' 'depression' 'memory' 'attention' 'cognitive'. We selected publications in English, French or Dutch, up to September 2014. Lists of references were searched for additional publications. In addition to clinical data, we collected the Summary of Product Characteristics as provided by pharmaceutical companies and consulted Dutch pharmaceutical sources (www.farmacotherapeutischkompas.nl, www.medicawiki.eu). Anticipating on using the level of evidence as a weighting factor for the algorithm, we graded the sources of information:

a. Cochrane-reviews (CR) and meta-analyses
b. Receptor occupancy profiles (Ki-values derived from the public Ki-database of the NIMH)
c. RCT's
d. Laboratory studies
e. Summaries of Product Characteristics (SPC)
f. Other public data in The Netherlands
g. Clinical experience of a panel of expert psychiatrists and researchers

2.2.3. Ranking the agents

For weighing the different items and decision support we used the The System of Objectified Judgement Analysis (SOJA), as described by Janknegt and Steenbroek[14]. We first extracted standardized effect sizes (standard mean differences, odd ratios or numbers needed to treat) from placebo controlled studies and (network) meta-analyses and ranked the agents accordingly. If standardized effect sizes were not available, best available evidence from e.g. systematic reviews was used. We formed categories containing agents of comparable effect sizes. We are aware that this results in a loss of information, but this enabled us to allocate agents without level a. evidence to a category when the next best evidence (such as agent-to-agent comparisons) suggested an equivalent effect size. Second, for some items (e.g. blunted affect), Ki-values for receptor affinities were the most consistent data for the rank order. We then used additional level d. data to create the cut off points between categories, adjusting biochemical information to

clinical practice. Third, the rank order of each category reflects the weight for the algorithm. We addressed agents to the lowest rank ('unknown/ambiguous'), when only level e. – g. data were available (SPC's or alike).

2.3. Building the algorithm and review of the clinical accuracy

The algorithm is described in the Results section. We formed a panel of five clinicians (IS, RS, MB, JO, JS), who reviewed four prototype test scenarios:

1. A dummy patient marking a 'very important' for the effectivity items and 'very unacceptable' for all side effects, showing the results of the optimal ratio of effectiveness versus tolerability.
2. A 'very important' for effectivity and a 'no answer/neutral' to all side effects, showing the results for the most effective agents regardless of side effects.
3. A 'very unimportant' for the effectivity criteria and a 'very unacceptable' for all side effects, showing the agents selected on the highest tolerability regardless of their effectivity.
4. A 'very important' for effectiveness on memory and attention and a 'no answer/neutral' to all other items, showing the agents most effective on cognitive functions regardless of side effects or effectiveness.

These test scenarios led to adjustments in the algorithm values of certain ranks, which are described in supplement A. Figure 1. summarizes the developmental phases of the process.

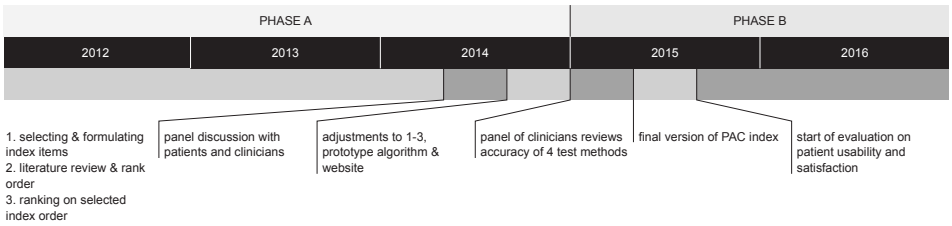

Figure 1. Phases of the PACindex development

3. Results

3.1. Selecting criteria for effective and tolerable antipsychotic medication

From the SRA-34, 23 items were selected and combined into 18 criteria (e.g. 'having difficulties in getting an orgasm' and 'having less sexual desire' were combined to 'sexual dysfunction'). We added supplementary questions on relative contraindications such as having a history of epileptic convulsions (see Table 1).

For each item, the user is asked how relevant (or acceptable) the described (adverse) effect is. On a 5-point Likert scale, options range from 'very acceptable' to 'absolutely not acceptable'.

Table 1: selected criteria of the PACindex (version 5.1)

1.	weight gain
2.	sexual dysfunction
3.	drowsiness
4.	hypersleep
5.	extrapyramidal side effects
6-9.	anticholinergic effects (blurred vision, urination difficulty, constipation, dry mouth)
10.	hypersalivation
11.	nausea
12.	dizziness
13.	get tired more quickly
14.	blunted affect and lack of creativity
15.	menstrual disorder
16.	effectiveness - overall change in symptoms
17.	effectiveness - depressive symptoms
18.	effectiveness - memory and attention problems
19.	way of administration
20.	additional questions concerning patient characteristics (smoking, history of epileptic convulsions)

3.2. Ranking antipsychotic medication on selection criteria

Below we subsequently describe the definition and the ranking for each criterion. Numbers correspond to the item order of the PACindex. Supplement A presents the questions, the weighting of the evidence and decision making.

1. Weight gain

Definition: weight gain as a continuous value.

Table 2: weight gain

category	name	sources
3	olanzapine SMD* 0.74	[15-18]
	clozapine SMD 0.65	[15-18]
2	quetiapine SMD 0.43	[15,16,18]
	risperidone SMD 0.42	[15,16,18]
1	amisulpride SMD 0.20	[15]
	perphenazine	[19]
	zuclopentixol	[20]; equals sulpiride and equals placebo
	pimozide	[21]; equals placebo
	aripiprazole SMD 0.17	[15,16]
	lurasidone SMD 0.11	[15]
	haloperidol SMD 0.09 NS	[15,18]
0**	Penfluridol	SPC: mentioned without indicating prevalence
	pipamperone	no data
	flupentixol	no data
	sulpiride	medicawiki: uncommon

**SMD = standard mean difference compared to placebo. ** Ranked: comparable to Haloperidol. 3 = strongest effect, 0 = ambiguous/insufficient data*

2. Sexual dysfunction

Definition: sexual dysfunction.

Table 3: sexual dysfunction

category	name	sources
4	risperidone SMD* 1.23	[15-18]
3	haloperidol SMD 0.70	[15-18]
	amisulpride	[22]; comp. to haloperidol and risperidone
	sulpiride	[23]; comp. to amisulpride
	flupentixol	[23]; comp. to haloperidol (being an FGA)
	perphenazine	[23]; comp. to haloperidol (being an FGA)
	pipamperone	[23]; comp. to haloperidol (being an FGA)
	zuclopentixol	[23]; comp. to haloperidol (being an FGA)
	pimozide	[23]; comp. to haloperidol (being an FGA)
2	olanzapine SMD 0.14	[15]
1	quetiapine SMD -0.05 NS	[15,24]; comp. to aripiprazole
	clozapine	[25]; comp. to quetiapine
	aripiprazole SMD -0.22 NS	[15]
	lurasidone SMD -0.34	[15]

**SMD = standard mean difference compared to placebo. Negative values indicate that the antipsychotic agent is favoured over placebo. 4 = strongest effect*

3. Drowsiness

Definition: drowsiness and getting slower as a result of the sedative properties of antipsychotic agents. The same ranking is used for side effect Sleep.

Table 4: drowsiness

category	name	sources
4	clozapine OR* 8.82 NNH** 2	[15,26]
3	quetiapine OR 3.76 NNH 4	[15,26]
	olanzapine OR 3.34 NNH 4	[15,25,18]; comparable to quetiapine
	perphenazine	H_1-receptor affinity 8 comp. to quetiapine 10
	flupentixol	H_1-receptor affinity 1 comp. to olanzapine 2
2	zuclopentixol OR 2.89 no NNH	[20] > placebo; H_1-receptor affinity unknown. Evidence level low
	haloperidol OR 2.76 NNH 5	[15,26]
	risperidone OR 2.45 NNH 6	[15,26]; comp. to haloperidol
	lurasidone OR 2.45 NNH	[15]
	pimozide	H_1-receptor affinity 359, comp. to haloperidol 1319
	pipamperone	H_1-receptor affinity 2400, comp. to haloperidol 1319
1	aripiprazole OR 1.84 NNH 10	[15,26]
	amisulpride OR 1.42 no NNH	[15,26]
0	penfluridol***	[27]; ambiguous. No data for H_1-receptor affinity
	sulpiride****	[28]; 'does not block H_1-receptor'

**OR = odds ratio compared to placebo. **NNH = number needed to harm. ***penfluridol ranked #3: comparable to haloperidol. ****sulpiride ranked #2: comparable to aripiprazol.*

4. Sleep

Definition: increased sleep or having difficulties waking up as a result of the sedative properties of antipsychotic agents.

Table 5: sleep

category	name	sources
4	clozapine OR* 8.82 NNH** 2	[15,26]
3	quetiapine OR 3.76 NNH 4	[15,26]
	olanzapine OR 3.34 NNH 4	[15,25,18]; comparable to quetiapine
	perphenazine	H_1-receptor affinity 8 comp. to quetiapine 10
	flupentixol	H_1-receptor affinity 1 comp. to olanzapine 2
2	zuclopentixol OR 2.89 no NNH	[20] > placebo; H_1-receptor affinity unknown. Evidence level low
	haloperidol OR 2.76 NNH 5	[15,26]
	risperidone OR 2.45 NNH 6	[15,26]; comp. to haloperidol
	lurasidone OR 2.45 NNH	[15]
	pimozide	H_1-receptor affinity 359, comp. to haloperidol 1319
	pipamperone	H_1-receptor affinity 2400, comp. to haloperidol 1319
1	aripiprazole OR 1.84 NNH 10	[15,26]
	amisulpride OR 1.42 no NNH	[15,26]
0	penfluridol***	[27]; ambiguous. No data for H_1-receptor affinity
	sulpiride****	[28]; 'does not block H_1-receptor'

**OR = odds ratio compared to placebo. **NNH = number needed to harm. ***penfluridol ranked #3: comparable to haloperidol. ****sulpiride ranked #2: comparable to aripiprazol.*

5. Extrapyramidal side effects

Definition: parkinsonism, rigidity, akathisia and tardive dyskinesia.

Table 6: extrapyramidal side effects

category	name	sources
6	haloperidol OR* 4.76	[15,18,25]
	flupentixol	D_2-receptor affinity 1 comp. to haloperidol 2
	perphenazine	D_2-receptor affinity 1 comp. to haloperidol 2
	penfluridol	SPC/(MedicaWiki): comp. to haloperidol; no data for D_2-receptor affinity
	zuclopentixol	SPC/(MedicaWiki): comp. to haloperidol; no data for D_2-receptor affinity
5	lurasidone OR 2.46	[15]
	risperidone OR 2.09	[15,25]
	pimozide	D_2-receptor affinity 6 comp. to risperidone 4
	pipamperone	[30]; comp. to risperidone
4	amisulpride OR 1.60	[15]
	sulpiride	D_2-receptor affinity 9.8 comp. to amisulpride
3	aripiprazole OR 1.20	[15]
2	quetiapine OR 1.01	[15,25]
	olanzapine OR 1.00	[15]
1	clozapine OR 0.3	[15,25]

**OR = odds ratio compared to placebo. 6 = strongest effect.*

6./7./8./9. Anticholinergic effects

Definition: we combined the different clinical expressions of anticholinergic activity: blurred vision, urinating difficulty, constipation, dry mouth (see supplement).

Table 7: anticholinergic effects

category	name	sources
4	clozapine	[31]: 27-250 dose-AA relation. M_1-affinity 12
3	olanzapine	[31]: 1-15 dose-AA relation. M_1-affinity 28
2	quetiapine	[31]: 1-5.4 dose-AA relation. M_1-affinity 303
1	pimozide	M_1-affinity 800
	lurasidone	[32]: M_1-affinity > 1000
	perphenazine	M_1-affinity 1496
	aripiprazole	[31]: dose-AA relation: zero. M_1-affinity 6778
	risperidone	[31]: dose-AA relation: zero. M_1-affinity 10.000
	haloperidol	M_1-affinity 10.000
	amisulpride	M_1-affinity > 10.000
	penfluridol	(MedicaWiki): "rare"
	flupentixol*	(MedicaWiki): "common"
	sulpiride	(MedicaWiki): "uncommon"
	pipamperone	(MedicaWiki): "rare"
	zuclopentixol	(MedicaWiki): "rare"

**flupentixol ranked #2: comparable to quetiapine. 4 = strongest effect.*

10. Hypersalivation

Definition: hypersalivation.

Table 8: hypersalivation

category	name	sources
5	clozapine 32.7%* (29-37)	[33]; 16, n = 559
4	zuclopentixol 24.2% (16-36)	[33]; 2, n = 53
3	haloperidol 18.4% (16-21)	[33]; 12, n = 1115
2	olanzapine 8.2% (7-10)	[33]; 5, n = 1857
	amisulpride 7.8% (4-14)	[33]; 5, n = 115
1	risperidone 5.7% (2-6)	[33]; 3, n = 325
0**	penfluridol	no data
	flupentixol	
	aripiprazole	
	lurasidone	
	sulpiride	
	perphenazine	
	pipamperone	
	quetiapine	
	pimozide	

**prevalence (standard deviation). **ranked #3 (mean weight) because of insufficient information.*

11. Nausea

Definition: nausea and/or vomiting.

Table 9: nausea

category	name	sources
2	aripiprazole clozapine	SPC: "common"; [34]; ARI > QUE, RIS SPC: "common"; [35]; OLA & RIS < CLO
1	olanzapine pimozide lurasidone	SPC: "common" SPC: "common" SPC: "common"
0*	sulpiride quetiapine risperidone haloperidol pipamperone zuclopentixol amisulpride flupentixol perphenazine penfluridol	SPC: "unknown"

**ranked #1 (mean weight) because of insufficient information: no evidence for a superior effect than olanzapine. 2 = strongest effect. ARI = aripiprazole; QUE = quetiapine; RIS = risperidone; CLO = clozapine.*

12. Dizziness

Definition: dizziness due to orthostatic hypotension.

Table 10: dizziness

category	name	sources
3	risperidone quetiapine clozapine haloperidol perphenazine aripiprazole	α_1-receptor affinity 3 α_1-receptor affinity 8 α_1-receptor affinity 8 α_1-receptor affinity 10 α_1-receptor affinity 10 α_1-receptor affinity 26
2	lurasidone olanzapine pimozide	[32]: α_1-receptor affinity 50 α_1-receptor affinity 57; 36; RR 0.51 vs FGA (significant after two years) α_1-receptor affinity 76
1	amisulpride	α_1-receptor affinity > 10.000
0*	penfluridol pipamperone flupentixol sulpiride zuclopentixol	no data

**ranked #2 (mean weight) because of insufficient information. 3 = strongest effect.*

13. Get tired more quickly

Table 11: get tired more quickly

category	name	sources
2	clozapine olanzapine quetiapine pimozide perphenazine risperidone haloperidol penfluridol flupentixol sulpiride pipamperone lurasidone	
1	aripiprazole	[34]

2 = strongest effect.

14. Blunted affect + Need for companionship

Definition: blunted affect is considered to be a secondary negative symptom (or: neuroleptic induced deficit syndrome)[37]. It is a subjective experience of emotional dampening.

Table 12: blunted affect + need for companionship

category	name	sources
2	haloperidol	D_2-affinity 2; [38]
	perphenazine	D_2-affinity 1
	lurasidon	[32]: D_2-affinity 1.6
	penfluridol	chemical compounds similar to haloperidol
	zuclopentixol	chemical compounds similar to haloperidol
	pipamperone	chemical compounds similar to haloperidol
	risperidone	D_2-affinity 4; [38]
	pimozide	D_2-affinity 6; [39]; affinity similar to haloperidol
	amisulpride	D_2-affinity 2
	sulpiride	D_2-affinity 10
1	olanzapine	D_2-affinity 31; [38,40]
	quetiapine	D_2-affinity 437
	clozapine	D_2-affinity 148
	aripiprazole	D_2-affinity 2; partial antagonism

2 = strongest effect on blunted affect/need of companionship.

15. Menstrual disorder (women only)

Table 13: menstrual disorder (women only)

category	name	sources
4	risperidone SMD* 1.23	[15,18]
3	haloperidol SMD 0.70	[15,18]
	amisulpride	[22]; comp. to haloperidol
	sulpiride	[23]; comp. to amisulpride
	flupentixol	[23]; comp. to haloperidol (being an FGA)
	perphenazine	[23]; comp. to haloperidol (being an FGA)
	pipamperone	[23]; comp. to haloperidol (being an FGA)
	zuclopentixol	[23]; comp. to haloperidol (being an FGA)
	pimozide	[23]; comp. to haloperidol (being an FGA)
2	olanzapine SMD 0.14	[15]
1	quetiapine SMD -0.05 NS	[15,24]; comp. to aripiprazole
	clozapine	[25]; comp. to quetiapine
	aripiprazole SMD -0.22 NS	[15]
	lurasidone SMD -0.34	[15]

**standard mean difference compared to placebo. 4 = strongest effect.*

16. Effectiveness - Overall change in psychotic symptoms

Definition: overall change in symptoms, assessed by the Positive and Negative Symptom Scale or the Brief Psychiatric Rating scale15.

Table 14: effectiveness - overall change in psychotic symptoms

category	name	sources
3	clozapine SMD -0.88*	[15]
2	amisulpride SMD -0.66	[15]
	olanzapine SMD -0.59	[15]
1	risperidone SMD -0.50	[15]
	haloperidol SMD -0.45	[15]
	penfluridol RR** 0.69	[27]; 'improvement global state' RR 0.69. similar to other FGA
	quetiapine SMD -0.44	[15]
	aripiprazole SMD -0.43	[15]
	lurasidone SMD -0.33	[15]
0***	flupentixol	[41]; 'no clear data on mental state and behaviour'
	sulpiride	[28]; 'no data for global outcomes'
	pipamperone	no clinical studies
	zuclopentixol	[20]; 'results not significant

**standard mean difference compared to placebo. **relative risk. ***ranked #1: comparable to haloperidol. 3 = strongest effect.*

17. Effectiveness - Depressive symptoms

Definition: Change in depression scores after antipsychotic treatment started16.

Table 15: effectiveness - depressive symptoms

category	name	sources
4	clozapine -0.51*	16
3	amisulpride -0.37	16
2	olanzapine -0.27	16
	quetiapine -0.23	16
1	aripiprazole -0.12	16
	risperidone -0.10	16
0**	haloperidol	SPC: 'often': depression as side effect
	lurasidone	
	penfluridol	SPC: not mentioned
	pimozide	SPC: 'very often': depression as side effect
	pipamperone	
	perphenazine	
	flupentixol	SPC: depression mentioned without prevalence
	zuclopentixol	
	sulpiride	

**Hedge's g, medium effect size as compared to haloperidol. **0 points: no favourable effect on depression. 4 = strongest effect.*

18. Effectiveness - Memory and attention problems

Definition: Change in cognitive functions, (verbal learning) memory and attention after antipsychotic treatment started.

Table 16: effectiveness - memory and attention problems

category	name	sources
1	olanzapine MDes -0.20*	42
	quetiapine MDes -0.20	
0***	haloperidol	42
	amisulpride	
	risperidone MDes NS**	
	flupentixol	
	perphenazine	
	penfluridol	
	zuclopentixol	
	pimozide	
	pipamperone	
	aripiprazole	
	clozapine	
	sulpiride	
	lurasidone	

**mean different effect size compared to haloperidol and amisulpride. **no significant difference in effect size compared to haloperidol and amisulpride. ***0 points: no favourable effect on cognition. 0 = neutral due to lacking information or inconsistent results. 1 = probably favourable effect.*

19. Ways of administration

Definition:

1. *Tablets daily,*
2. *1-2 tablets per week,*
3. *Fluid administration daily,*
4. *Depot injection.*

Table 17: ways of administration

category	name	sources
1	quetiapine clozapine perphenazine amisulpride pimozide aripiprazole pipamperone flupentixol sulpiride lurasidone	(Farmacotherapeutisch Kompas)
2	penfluridol	
3	zuclopentixol haloperidol pipamperone sulpiride	
4	haloperidol olanzapine risperidone perphenazine zuclopentixol aripiprazole flupentixol	

20. Additional questions concerning patient characteristics

a. cigarette smoking

This item is not included in the algorithm, instead a remark is made in the final advice on the occurrence of blood level rising in clozapine, possibly requesting dose adjustment.

b. epileptic seizure

Definition: yes or no.

Table 18: epileptic seizure

category	name	sources
4	clozapine SIR* 9.5/9.00%**	[44/45]
3	quetiapine SIR 2.50/5.90%	[44/45]
	olanzapine SIR 2.05/4.91%	[44/45]
2	zuclopentixol 4.18%	[45]
	risperidone 3.68%	[44/45]
	pimozide 3.40%	[46]; SPC: caution, 'grand-mal convulsions rep.'
	haloperidol 3.27%	[45]
	perphenazine 3.19%	[45]; SPC: extra caution, is a phenothiazine
	flupentixol 2.58%	[45]
	aripiprazole 2.59%	[45]
1	sulpiride 0.5%	[46]
0***	pipamperone	no data
	amisulpride	SPC: 'uncommon'
	lurasidone	SPC: 'use cautiously', no further data

**standardized incidence ratio. **% convulsions of total no. of adverse drug reactions. ***ranked #2: comparable to perphenazine.*

c. wish to become pregnant or to lactate

We concluded that the indication for antipsychotic medication during pregnancy and lactation depends on factors that necessitate an individual risk assessment. Online self-assessment is unsuitable here. The inclusion of this criterion was suggested by the patient panel. In case a patient has a pregnancy wish, she will be informed about this viewpoint and provided with information links. The rank order of this item will not contribute to the final advice.

Developing the PACindex algorithm

For the items 1 to 18, the rank order of the antipsychotic agent is divided by the number of ranking levels. The result is the proportional rank (Figure 2). For example, for "weight gain", amisulpride has rank 1 out of 3 ranking levels, indicating that amisulpride leads to mild weight gain (in comparison to e.g. olanzapine, on rank 3). The proportional rank of amisulpride is 1/3 = 0.333. The proportional rank is multiplied by the relevance rating provided by the respondent, resulting in the individual weight of the associated item. The relevance rating ranges from 0 (very acceptable) to 4 (very unacceptable). In the example of amisulpride, if the respondent indicates that "weight gain" is "very unacceptable", the weight for amisulpride is 0.333 * 4 = 1.333.

In order to calculate the overall score of an agent, all side effect weights are summed and multiplied by -1, so that side effects reduce the score. Effectiveness

weights are multiplied by +4 (psychotic symptoms, depressive symptoms) or +2 (memory improvement) to allow for the importance of the therapeutic effects. In order to prevent scores below 0, all scores are increased by +70.

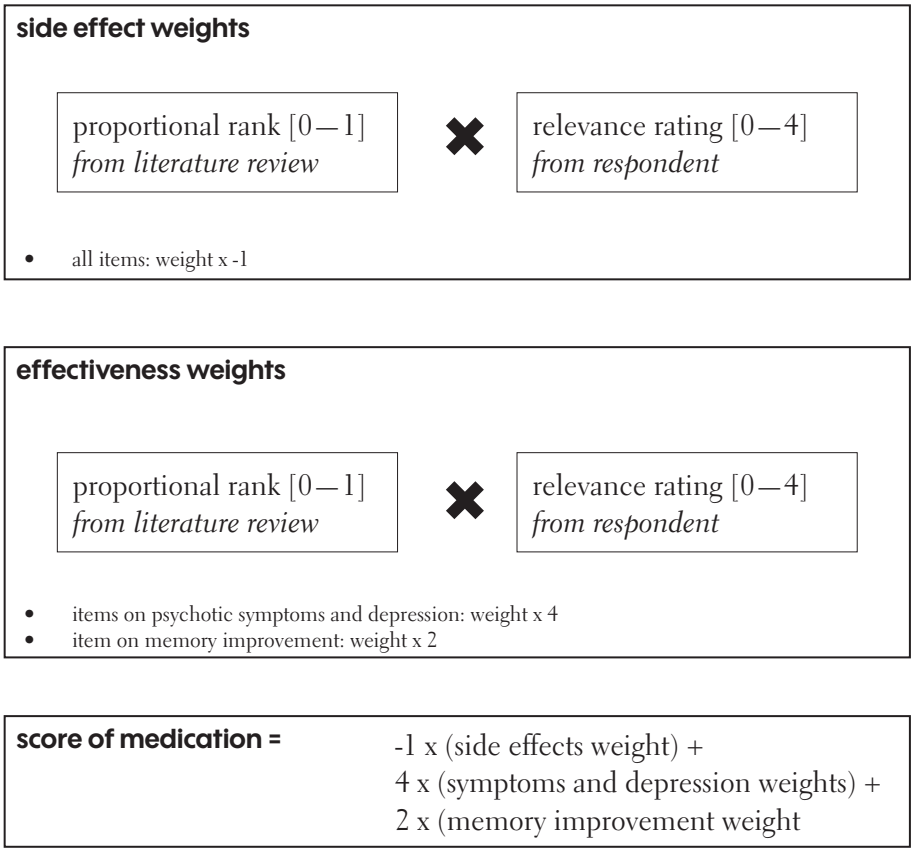

Figure 2: Schematic representation of the PACindex scoring algorithm

The rank '0'('unknown/ambiguous') from the literature review was created for the antipsychotic agents that did not have sufficient data (e.g. data on weight gain caused by penfluridol, pipamperone, sulpiride and flupentixol). However, 'lack of scientific evidence' does not imply 'no meaningful clinical effect'. We have chosen two strategies: the proportional ranking of a biochemical counterpart with enough evidence was assigned, if the antipsychotic has a comparable propensity to produce the given (adverse) effect. In absence of a biochemical counterpart, the proportional rank agent is defined as the arithmetic mean proportional rank of the group. The results for all of the antipsychotic medications are presented in a chart (see Figure 3).

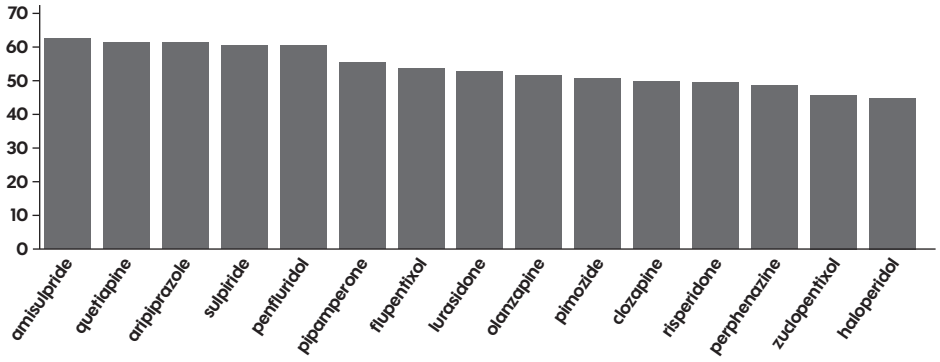

Figure 3. Example of the final chart (random test result)

4. Discussion

We created a transparent ranking process for the most frequently prescribed antipsychotics in the Netherlands based on their reported adverse effects and effectiveness. The ranking process enabled us to create the algorithm for an online decision aid: the PACindex. In cooperation with patients we selected a list of criteria of effects and adverse effects based on the SRA-34. A review of the current literature formed the basis of the algorithm.

The quality of available evidence varied widely across the 20 criteria. The items weight gain, sexual dysfunction, menstrual disorder, extrapyramidal symptoms and effectiveness on psychotic symptoms were most extensively researched. We were able to rank at least 5 antipsychotic agents based on effect sizes from meta-analyses or systematic reviews (OR's, SMD's, NNH). These data were used as an indicator for the relative position of an antipsychotic agent, to which the remaining agents with data from, for example, RCT's were compared.

For the ranking of antipsychotic agents concerning their propensity to cause drowsiness, sleep, hyper salivation, nausea, dizziness, tiredness, blunted affect/need of companionship, effectiveness on depressive symptoms, effectiveness on memory and attention, only lower level evidence was available (open-label studies, single dose studies, descriptive reviews or receptor binding coefficients). These items were individually brought to discussion in a group of expert psychiatrists and researchers, which led to adjustments in the algorithm weights.

Some important limitations need to be mentioned. The lack of standardized effect sizes for the aforementioned criteria may have induced errors or counter-intuitive results in the ranking of medications. Counter-intuitive results may also be related to clinician biases or preferences. We used evidence from RCT's, although these studies are sometimes subject to non-representative patient samples. Although network meta-analyses do not solve the potential problem of non-representative patient samples, network meta-analyses offer the best available evidence when separate head-to-head comparisons are lacking. Since the current research is focusing on the development of new agents rather than re-evaluating adverse effects of existing agents, we do not expect that more conclusive evidence will become available in the near future. In the current version of the PACindex the weighting of different effects or adverse effects in the PAC scoring algorithm is arbitrary. We have chosen to value symptom reduction most strongly, since improving symptomatic outcome is the main goal of treatment with antipsychotic medication. However, we would like to emphasize that patients can put weight on their preferences ('Do I value effect in psychotic symptoms over weight gain?') by assigning a score 1 to 5 per criterion. But still the weighting we assigned in the current version of the PACindex tool is arbitrary and open to debate. Another important limitation is that the evidence on the occurrence of (adverse) effects is at the group level. We are only able to provide patients and clinicians with an estimation of the relative likelihood that adverse effects or effects will occur. As a third potential limitation, users of the PACindex might interpret the feedback on antipsychotics they receive as a direct advice. Therefore, on the results page of the PACindex, we emphasize that the tool does not replace clinical counselling.

The ambiguous data for pregnancy and lactation risks made us decide to leave this criterion out of the ranking. We considered the evidence concerning these important decisions too complex to mention in our tool. Here consultation with a clinician is absolutely needed.

An important strength of the PACindex is that it is the first online tool to prepare patients for making informed decisions on antipsychotic medication use based on the outcomes of all available scientific research. The PAC tool will be presented on a separate website, and advocated by both patient organizations and clinicians. Patients are encouraged to use the website together with their clinician or use the tool individually and discuss the results with their clinician. For the latter group of users, we indicate that the results are meant to be used in a shared decision process and do not replace clinical counselling. Users can download an overview of the ranking and literature review per criterion. On the

results page, patients can access the information leaflet of each antipsychotic agent by clicking on the corresponding bars of the plot (see Figure 2). In some countries outside the Netherlands, online patient decision aids are considered medical devices, subject to specified legislation on monitoring and patient safety. However, the user instructions and disclaimer discussed here and presented on the website comply with Dutch legislation. We have not assessed to what extend the PACindex in its current form is compatible with legislation in countries outside the Netherlands. For clinicians and researchers, the personal rank order provides a valuable insight in patients' preferences, which can serve as a starting point for the conversation about effects and potential side effects of antipsychotic medication. We expect to enhance medication adherence by both stimulating shared decision and considering patients' preferences before clinical counselling, as is shown before[47]. Evaluation of this hypothesis in a randomized controlled trial is needed. When new evidence is available, future refining will be possible. Moreover, feedback form clinicians or patients may be considered in re-evaluation of the ranking order of antipsychotic medication and may diminish possible counter-intuitive results. Currently, we are evaluating the usability, patient satisfaction and overall appreciation of the tool. These data are not yet available. In conclusion, we have developed an online tool connecting scientific research to personal treatment strategies, enhancing empowerment of people with a psychotic disorder.

The PACindex (in Dutch only) can be visited at htts://www.pakwijzer.nl

Contributors

All authors contributed to the study design and interpretation of the results. FD contributed to the literature search, ranking procedure, and writing of the report. IW contributed to the ranking procedure, the interpretation of comments of consulting clinicians, and the writing of the report. MB contributed to building the algorithm and writing the report. IS contributed to the literature search and ranking procedure. LH developed the PAC Index, contributed to the ranking procedure and building the algorithm, and supervised the study. All authors participated in critical revision of manuscript drafts and approved the final version.

Conflict of interest

Prof. dr. L. de Haan has received an investigator initiated grant from Eli Lilly and Janssen-Cilag, more than 3 years ago. We have no other potential conflict of interest, financial or otherwise, related to the submitted work.

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Supplement to Chapter 2

1. Weight gain

Q: How acceptable is it if you would gain weight due to your antipsychotic medication?

Considerations concerning the ranking:
We have mainly used the results of the meta-analysis of Leucht et al.[1], the meta-analysis of Bak et al.[2] who also examined duration of antipsychotic use, complemented with two Cochrane reviews on pimozide and zuclopenthixol[3,4], and effects of olanzapine on M_3-receptor (increased the risk on weight gain and diabetes), a regular review[5] and a clinical trial for perphenazine[6]. We have not used the singular results of the CATIEtrial, as they were incorporated by Bak et al.[2]. Although Bak showed an increased risk on weight gain for haloperidol and first generation antipsychotics on the long term (up to 38 weeks), it was decided to rank haloperidol based on the study of Leucht et al because they excluded non-blinded studies. This implies that the rank order below is mostly based on relative short term effects of antipsychotic medication on weight gain (6 weeks after start).

For penfluridol, pimpamperone, flupentixol and sulpiride we have not been able to find clinical data, they have therefore been listed as 'ambiguous/insufficient'.

2. Sexual dysfunction

Q: How acceptable is it if you would experience less desire to make love or have problems to have an orgasm due to your antipsychotic medication? How acceptable would it be for you if your erection becomes less strong?

Considerations concerning the ranking:
Sexual dysfunction is related to increased levels of prolactin and is dependent on antagonism of several receptor systems[7]. Prolactin levels rise as a result of dopamine blockade in the hypothalamus-pituitary axis, where dopamine activity inhibits the release of prolactin. A second important factor is an antipsychotic's capacity to pass the blood-brain barrier. The pituitary gland lies outside the blood brain barrier and is therefore impacted by peripheral active metabolites of antipsychotics. Risperidone and amisulpride are medications that pass the blood brain barrier poorly and have a limited central-to-peripheral ratio, therefore they are associated with significant prolactin level increases[8].

In order to rank the agents, we have used the results of Leucht et al.[1], complemented with results of two reviews[9,10]. Amisulpride has not been studied as consistently on clinical outcomes related to hyperprolactineamia as risperidone. Although several reviews[9,11,12] claim amisulpride to have at least an equivalent effect on prolactin levels, they do not show an insightful comparison (with numerical data) to either haloperidol or risperidone. We have therefore decided to approach the claims conservatively and rank amisulpride together with haloperidol, until future clinical results state otherwise.

3. Drowsiness

Q: How acceptable is it if you get drowsy or slow due to your antipsychotic medication?

Considerations concerning the ranking:
Considerations are presented in table.

Adjustments in the algorithm value after running test scenarios 3 (see Results section). Penfluridol was given the same value as haloperidol due to their similar biochemical compounds. Sulpiride, of which we only know that it does not block the H_1-receptor[13], was given the value of the other non-H_1-blocking agents aripiprazole and amisulpride, of which we did have a OR and NNH[1,14].

4. Sleep

Q: How acceptable is it if you sleep more or have more difficulty waking up due to your antipsychotic medication?

Considerations concerning the ranking:
Considerations are presented in table.

Adjustments in the algorithm value after running test scenarios 3 (see Results section). Penfluridol was given the same value as haloperidol due to their similar biochemical compounds. Sulpiride, of which we only know that it does not block the H_1-receptor[13], was given the value of the other non-H_1-blocking agents aripiprazole and amisulpride, of which we did have a OR and NNH[1,14].

5. Extrapyramidal side effects

Q: How acceptable is it if you would experience muscle stiffness, tremors or restless movements due to your antipsychotic medication?
Note: EPS is a dose-related effect of antipsychotics.
Considerations concerning the ranking:

We have based the ranking primarily on Leucht's meta-analysis of 2013. For missing data, we have used evidence concerning D_2-receptor affinities of agents. Taken together with the notion that EPS are a dose dependent phenomenon, also occurring in rodents treated with agents with a low D_2-affinity at high dosages[15] we consider D_2-receptor affinities as an optimal estimation of the propensity to induce extrapyramidal side effects. Herewith we ignore the possible effects of 5HT2a-antagonism, intrinsic anticholinergic properties and multireceptortheories[16,17].

6./7./8./9. Anticholinergic effects

Q: How acceptable is it if you will...
... have blurred vision…
... be urinating less smoothly…
... get constipated more often…
…have a dry mouth more often…
due to your antipsychotic medication?

Considerations concerning the ranking:
Since various factors, such as smoking and concomitant medication, influence anticholinergic signalling in the human body, in addition to antipsychotic medication, the receptor affinity (Ki-value) of an antipsychotic agent does not necessarily represent the clinical anticholinergic effect or side effect.

Muscarinic effects of antipsychotic agents can be assessed by the anticholinergic activity (AA). Chew et al. have described a model for an estimated dose-AA relationship of six antipsychotics[18]. Their procedure examines the amount of displacement of the muscarinic receptor antagonist titrated quinuclidinyl benzilate (3H-QNB) caused by compounds present in an individual's serum (or plasma). The effect of the antipsychotic agent was compared to a standardized atropine curve. Peripheral AA was correlated with serum levels of anticholinergic medications as well as AA in cerebral spinal fluid. The concentrations of atypical antipsychotics were based on typical serum or plasma drug levels and pharmacokinetic data were used to calculate an estimated dose-AA relationship[18].

We considered this to be to best step towards translation of Ki-values to clinical aspects.

Clinical data to support these frameworks are incomplete due to under-reporting in trials[19], and some reviews[5,20] do not give insight into the ranking of anticholinergic properties per agent, because they do not mention their sources

with enough insight[19]. This makes comparison between antipsychotics difficult. The use of high dosages of FGA, mainly haloperidol and zuclopenthixol[21] flaws their results, as well as their inability to obtain information on concomitant use of anticholinergics[22].

We have decided to position clozapine, olanzapine and quetiapine on a relative distance to each other based on the anticholinergic action described by Chew, leaving the remaining agents in the 'rare' category. The cut off point for the 'rare' category was created by using the Ki-value of the M_1-receptor of ziprasidone (an agent not included in our index). Chew et al. mention two Ki-values for ziprasidone: the one found by Bymaster et al. (300 nM)[23] and Schmidt et al. (5100 nM)[24]. We have averaged these values to +/- 2700 nM. With regard to the lower limit of 300 nM and still a zero AA-dose, whereas quetiapine has a fixed affinity of 303 nM and a AA-dose relation of 1-15, we propose that the cut-off point must lie somewhat above 300nm (e.g. 400nM). Following this assumption, we have ranked pimozide (800 nM), lurasidone (>1000)[25] and perphenazine (1496), together with ziprasidone (2700 nM) and aripiprazole (6778 nM). Of penfluridol and pipamperone we have no data. They are grouped according to their comparability to haloperidol in M_1-receptor affinity. Flupentixol is given the same rank as quetiapine due to explicit mention of anticholinergic effects in the MedicaWiki initiative and the Summary of Product Characteristics.

This means we have left out a review focusing on constipation from De Hert and colleagues[26]. Although they underscore the seriousness and high prevalence of constipation, they conclude that it is rarely studied and under-reported and strengthen the need for further research. Constipation is thought to be caused via caused by antihistaminergic and antidopaminergic pathways[26]. If further clinical evidence emerges, constipation might be separated from the other anticholinergic effects.

10. Hypersalivation

Q: How acceptable would it be if you produced more saliva due to your antipsychotic medication?

Considerations concerning the ranking:
We have used the work of Ozbilen and colleagues[19], which provided numerical data.

Adjustments in the algorithm value after running test scenarios 3 (see Results section). The algorithm values of rank 0 (meaning no data available) were given the value of the mean value of the item.

11. Nausea

Q: How acceptable is it if you would experience nausea more often due to your antipsychotic medication?

Considerations concerning the ranking:
It is unclear what mechanisms cause nausea associated with the use of antipsychotic agents (suggestions for clozapine include delayed gastric emptying due to anticholinergic effects or increased appetite due hypersalivation[27]). Ranking by receptor affinity therefore was not possible. Ranking was based on the information of Summary of Product Information. We subsequently used the significant results from Cochrane Reviews to subdivide aripiprazole and clozapine from the rest and to categorize olanzapine and pimozide as agents with less propensity to induce nausea.

Adjustments in the algorithm value after running test scenarios 3 (see Results section). The algorithm values of rank 0 (meaning no data available) were given the value of the mean value of the item

12. Dizziness

Q: How acceptable is it if you would experience dizziness more often due to your antipsychotic medication?
Note: dizziness is often a dose-related effect of antipsychotics.

Considerations concerning the ranking:
We have decided to rank the agents on their affinity for the adrenergic α_1-receptor, being the associated receptor system of orthostatic mechanisms in, for example, clozapine[28]. Outcomes from clinical data, retrieved from Cochrane Reviews and reviews, encounter too much heterogeneity[29] and ambiguity[30].

Within the clinical trials, we then have given preference to Cochrane Review of Duggan et al.[31] on olanzapine. Only olanzapine shows significantly less dizziness than FGA after two years of treatment[31]. The confidence intervals on other antipsychotic agents from the study of Edwards et al.[30] are broad and therefore more imprecise. The results of the Cochrane reviews on the other antipsychotic agents also have confidence intervals that surpass the 1.0 value. We decided to use the clinical data of olanzapine to create a cut-off point in distinguishing the

α_1-receptor affinities that are more likely associated with dizziness in clinical practice. Lurasidone is placed in the same category as olanzapine since the difference in Ki-value is small.

Adjustments in the algorithm value after running test scenarios 3 (see Results section). The algorithm values of rank 0 (meaning no data available) were given the value of the mean value of the item.

13. Get tired more quickly

Q: How acceptable is it if you would get tired more quickly due to your antipsychotic medication?

Considerations concerning the ranking:
Fatigue is an under-researched topic, with heterogeneity between studies. Studies often only reported 'fatigue' when it occurred in at least 5% of the study population[32]. Results of a Cochrane review[32] show a trend for aripiprazole to be favoured over other second generation antipsychotics. The large confidence intervals are probably due to the fact that per study arm few (<50) participants were included.

Since this is the only source, we have decided to rank aripiprazole as the antipsychotic drug with the least probability to induce fatigue.

Adjustments in the algorithm value after running test scenarios 3 (see Results section). The algorithm values of rank 0 (meaning no data available) were given the value of the mean value of the item

14. Blunted affect + Need for companionship

Q: How acceptable is it if you become flatter, less creative and less interested in companionship due to your antipsychotic medication?

Considerations concerning the ranking:
Despite this rather narrow description, feelings of emotional blunting have not been assessed in a similarly restricted manner. Therefore, as a general approach we searched for studies on general subjective well-being. It has been suggested that SGA, specifically, show an elevated level of subjective well-being than FGA[33]. 'Affect' and the feeling of being less creative are however not entirely covered by the traditional distribution of SGA being superior to FGA. Only a few clinical studies exist, that systematically researched 'affect': two double blinded RCT's[33,34] and one open label, semi-randomized clinical trial[35]. They

concern olanzapine, Risperidone and haloperidol (and other FGA's). Olanzapine is favoured over haloperidol in one of them[33], one other found no difference between olanzapine and risperidone[34]. De Haan et al. showed that D_2-occupancy between 60-70% is optimal for subjective well-being[36]. Next to this, a naturalistic study focusing on positive and negative effect on 'affect' favours olanzapine over risperidone and haloperidol[37].

Meagre evidence exists (derived from different study designs) that risperidone also causes secondary negative symptoms among which 'avolition'. Mas et al. and Artaloytia et al.[38] demonstrated this in RCT's with healthy individuals after controlling for EPS and sedation. This was a single dose administration design. Also, an open-label study showed that olanzapine did better than clozapine and risperidone on 'social integration[35]. However, these study designs do not reflect a systematic method and do not provide an explanation for the underlying cause.

Secondly, we propose a rationale for the occurrence of secondary negative symptoms. Secondary negative symptoms are suggested to be the logical result from treatment of positive symptoms by antipsychotic agents. By reducing cognitive biases seen in patients, like jumping to conclusions and having overconfidence in memory, patients experience increasing doubt and loss of decisiveness. Simultaneously, dampening hypersalience hence causes a subjective feeling of indifference towards stimuli and a loss of creativity and social contacts[8,39]. For 'blunted affect' we have used clinical results for 'negative affect' as circumstantial evidence. Subjective well-being is associated with D_2-receptor binding. This is not a linear effect, as lower D_2-binding is associated with more psychotic symptoms and results in a reduced motivational tone, whereas as higher D_2-receptor occupancy causes less reward from stimuli, resulting in flattened emotions (due to blocking D_2-receptors in the striatal region). This is supposedly explained by the fact that some agents bind looser to the D_2-receptor (e.g. olanzapine) than others (haloperidol, but also risperidone)[37]. In addition to this mechanism, Meltzer and colleagues underline the importance of serotonergic receptor binding and relative low D_2-/D_3-antagonism as a characteristic of 'atypical antipsychotics', but they do not provide robust clinical results pertaining to the effect on emotional well-being (depressive symptoms excluded), or more broadly, to secondary negative symptoms[16]. We therefore propose to rank the agents based on:

1. Their D_2-affinity being similar or less than that of dopamine (1.5 nM)[40] and
2. Their function as an agonist or antagonist of dopaminergic neurotransmission (e.g. aripiprazole).

15. Menstrual disorder (women only)

Q: How acceptable is it if your period occurred less often due to your antipsychotic medication?

Considerations concerning the ranking:
Antipsychotic-induced hyperprolactinaemia is associated with menstrual disturbances[41]. Prolactin levels rise as a result of dopamine blockade in the hypothalamus-pituitary axis, where dopamine activity inhibits the release of prolactin. A second important factor is an antipsychotic's capacity to pass the blood-brain barrier. The pituitary gland lies outside the blood brain barrier and is therefore impacted by peripheral active metabolites of antipsychotics. Risperidone and amisulpride are medications that poorly pass the blood brain barrier and have a poor central-to-peripheral ratio. As a result, they are associated with a significant increase in prolactin levels[8,42].

In order to rank the agents, the results by Leucht et al. were used[1], complemented with results of two reviews[9,10]. Amisulpride has not been studied as consistently on clinical outcomes related to hyperprolactinaemia as risperidone. Although several reviews[9,11,12] claim amisulpride has at least equivalent effects on prolactin levels, they do not show an insightful comparison (with numerical data) to either haloperidol or risperidone. We have therefore decided to approach the claims conservatively and rank amisulpride together with haloperidol, until future clinical results state otherwise.

The same ranking has been used for item Sexual dysfunction.

16. Effectiveness - overall change in symptoms

Q: Antipsychotics differ slightly in how well they work. Some agents are more effective than others. How important is it for you that an antipsychotic reduces your psychotic symptoms as much as possible?

Considerations concerning the ranking:
We mainly used the data by Leucht and colleagues[1], complemented with a Cochrane review of penfluridol[43]. For flupentixol, sulpiride, pipamperone and zuclopentixol we could not identify clear data. They have been ranked 'ambiguous/insufficient'.

Adjustments in the algorithm value after running test scenarios 1 and 2 (see Results section). We have added the agents of which we had no numerical data, to the least effective rank of agents of which we did have numerical data. So it was

avoided that 'no data' meant 'no effect'. Also, to reflect the effectiveness of clozapine relative to the other agents, it got an algorithm value of 18 as compared to 6 for the second ranking group of olanzapine and amisulpride and 5 for the remaining agents in ranking group 3 (data not shown).

17. Effectiveness - Depressive symptoms
Q: How important is it for you that an antipsychotic improves your depressive symptoms as much as possible?

Considerations concerning the ranking:
We have used the data of Leucht and colleagues[14]. Since then, no randomized trial or review on this topic has been published. For haloperidol and zuclopentixol, we have used data from the Summary of Product Characteristics. Of the remaining first generation agents we could not identify clear data. They have been ranked 'ambiguous/insufficient information'.

Adjustments in the algorithm value after running test scenarios 1 and 2 (see Results section). The group of agents without numerical data got an algorithm value of 2, as compared to a 3 for the least effective group.

18. Effectiveness - Memory and attention problems
Q: How important is it for you that an antipsychotic improves your memory and concentration problems? Or how important is it that an antipsychotic does not further impair your memory and concentration problems?

Considerations concerning the ranking:
Disturbance in cognitive functions such as working memory, attention and executive function is caused by blockade of D_2-, M_1-, H_1- and α_1-receptors[44]. The effects of antipsychotic treatment have been meta-analyzed by Désamericq et al.[45] who found significant differences on sub-domains (such as working memory and attention) of various agents compared to haloperidol. It would be most convenient to use these outcomes to rank the available agents to this report. However, it should be emphasized that open-label studies were included and that some studies used very high doses (>24mg) of haloperidol. Moreover in these studies different cognition measurements and time intervals were used in comparison to controls generally lacked. It is therefore the question whether the results are representative and can be generalized for clinical use. Since there is no placebo comparison for haloperidol, we have decided to address a positive

effect on these cognitive factors for olanzapine and quetiapine. Yet we leave a 'neutral' label to haloperidol and the rest, as to avoid that lack of proper data results in 'negative' properties.

It is unclear to what extent dosage of antipsychotics affect cognitive decline. It has been studied cross-sectionally[46,47] and also prospectively by Husa et al.[48]. The latter could not make a distinction between FGA and SGA due to methodology. Until more clinical studies in a prospective study design and with a large enough sample size have been published, we remain with the ranking based on the results of Désamerique et al.

19. Ways of administration

Q: What kind of administration do you prefer?

1. *Tablets daily*
2. *1-2 tablets per week*
3. *Fluid administration daily (droplets and/or grinded and dissolved tablets)*
4. *Depot injection (ranging from every fortnight to every 6 weeks)*

Considerations concerning the ranking:
Considerations are presented in table.

20. Additional questions concerning patient characteristics

Q: Have you ever suffered an epileptic seizure?

1. *Yes (advice: reconsider group 3 and 4)*
2. *No*

1. Epileptic seizure

Considerations concerning the ranking:
Data for ranking antipsychotic agents was retrieved from three published studies. Alper et al.[49] reviewed data on report of seizure incidents retrieved from phase II and III trials (clinical and pre-clinical) of Basis of Approval Reports USA. Only clozapine, quetiapine and olanzapine significantly showed a higher standardized incidence risk ratio. Secondly, we combined the results of Kumlien et al.[50] and Lertxundi et al.[51], who have used drug reaction databases of the WHO and Spain (Basque country). They counted the percentage of insults of the total spontaneously reported adverse drugs event per antipsychotic agent. This is an indirect and highly biased form of retrieving data, however it came closest to actual data of incidence. There have been no corrections for ways of

administration or dosage. We judged the results of Kumlien as more important than those of Lertxundi due to their larger dataset. The findings of Kumlien were in line with those of Apler.

2. Wish to become pregnant and to lactate

Considerations concerning the ranking:
Limited research was available for ranking. Guidelines on pregnancy while using antipsychotic medication were studied, namely the RIVM (Dutch National Institute for Public Health and the Environment) and the GGZ Trimbos Instituut (a national mental health institute) guidelines[52] based on a literature study of Gentile[53]. They conclude:

- Only prescribe antipsychotic medication to pregnant women on strict indication;
- If a psychosis occurs during pregnancy, and no antipsychotic drug is used, best prescribe first generation antipsychotics;
- Possible weight gain due to antipsychotic drugs olanzapine, quetiapine and risperidone may increase on risk foetal malformations;
- If a woman becomes pregnant while using antipsychotic medication, it is advised to continue the current drug instead of switching medication. The risk of switching is considered higher than possible differences between agents in teratogenic or other effects;
- Consider to discontinue antipsychotic medication at the end of pregnancy to decrease risk on extrapyramidal effects and insults on the neonate. This must be weighed against the risk on recurrence of the psychosis.

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CHAPTER 3

Objective: Dopamine D_2-receptor blockade by antipsychotic medication reduces psychotic symptoms but may reduce subjective well-being. The current study aims to further explore the relation between dopamine D_2-receptor affinity and subjective well-being within a large sample of patients with psychotic disorders.

Method: Patients participated in a longitudinal naturalistic cohort study: the Genetic Risk and Outcome of Psychosis (GROUP) study. Three groups of antipsychotic medication were formed based on their affinity for the D_2-receptor: 1. loose or partial agonistic binding, 2. moderate binding and 3. tight binding. Subjective well-being was assessed with the Subjective Well-being under Neuroleptics scale at baseline and 3-year follow up. Additionally, we compared changes in SWN scores when switching to a more 'loose or partial agonistic' binding agent or to a 'tighter' binding agent between baseline and 3-year follow-up.

Results: The final group consisted of 388 patients at baseline and 290 at 3-year follow up. No significant differences in SWN scores between the three affinity groups were found at baseline and 3-year follow up. Additionally, analyses yielded no significant changes in SWN scores after switching to a more 'loose or partial agonistic' or more 'tight' binding antipsychotic agent.

Conclusion: We did not find further support for the hypothesis that subjective well-being is associated with antipsychotics affinity for dopamine D_2-receptors. This might imply that the effect of antipsychotic D_2-receptors binding on subjective well-being is not large enough to be detected in this cross-sectional study. Other factors besides dopamine antagonism are probably more relevant for subjective well-being.

DOPAMINE D_2-RECEPTOR AFFINITY OF ANTIPSYCHOTICS IN RELATION TO SUBJECTIVE WELL-BEING IN PATIENTS WITH A PSYCHOTIC DISORDER

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IN: INTERNATIONAL CLINICAL PSYCHOPHARMACOLOGY,
32 (2017), 249-255

Introduction

Antipsychotics are the indicated pharmacological treatment for psychotic disorders[1]. Although antipsychotics are often effective in reducing positive symptoms (hallucinations, delusions), a range of impairing adverse effects often occur[2]. For instance, antipsychotics may induce the so called 'secondary negative symptoms', such as blunted affect, which can be detrimental to the subjective well-being of patients[33]. Subjective experiences related to antipsychotic medication is defined by De Haan[4] as "All experiences patients report, whether positive or negative, at the physical, emotional and cognitive levels, related to antipsychotic medication". The subjective adverse response to antipsychotic medication is considered a risk factor for medication non-adherence[3]. The risk of relapse after discontinuing antipsychotic medication is up to 80%[5]; therefore enhancing subjective well-being of patients using antipsychotics is of great importance.

Positive symptoms of psychosis are explained by excessive dopaminergic neurotransmission in the striatum and mesolimbic system which leads to a disturbed salience to neutral events or stimuli[6]. Antipsychotic medication occupies the dopamine D_2-receptor resulting in reduction of dopaminergic neurotransmission and thereby gradually diminishing positive symptoms[6]. D_2-receptor occupancy of antipsychotic agents is thus necessary for antipsychotic response. However, De Haan et al.[7] showed that higher D_2-receptor occupancy is also associated with decreased subjective well-being, as assessed using the Subjective Well-being under Neuroleptics scale (SWN;[8]). This finding has been replicated in two subsequent studies[9,10]. An explanation for this reduced well-being is that blockage of the dopamine receptor is also associated with reduced motivation and emotional experience on natural rewards; processes that were found to be related to endogenous dopaminergic activity[6]. This explanation raised the question whether there is an 'optimal' degree of blocking the D_2-receptor, finding balance between optimal reduction of positive symptoms of psychosis, as well as sustaining sufficient endogenous dopaminergic neurotransmission. De Haan et al.[11] demonstrated that D_2-receptor occupancy of 60-70% might be optimal in reducing symptoms as well as preserving subjective well-being of patients with recent-onset schizophrenia, showing the importance of low dosing of antipsychotics.

Antipsychotic agents differ in their affinity for the dopamine D_2-receptor, as indicated by the Ki-value[12]. Antipsychotics with D_2-receptor affinity similar to dopamine (1.5 nM) bind tightly to the D_2-receptor, whilst antipsychotics with lower D_2-receptor affinity (than dopamine) (such as clozapine (148 nM) and quetia-

pine (437 nM)), bind looser than dopamine and allow higher levels of endogenous dopaminergic transmission[12]. The association of antipsychotics D_2-affinity with well-being of patients was studied by Lataster and colleagues[13]. They compared the effects of a looser binding antipsychotic agent (olanzapine) with two tight binding antipsychotic agents (haloperidol and risperidone) on emotional experience. The Experience Sampling Method (ESM), an ecologically valid method to assess experiences, was used to measure positive and negative affect in daily life of patients to quantify well-being. In more tight binding antipsychotics, they found less positive affect and more negative affect at higher estimated D_2-receptor occupancy levels in comparison with lower estimated occupancy levels. For olanzapine this effect was not found. These findings suggest that the degree of D_2-receptor occupancy is particularly of influence on emotional experience for tight binding antipsychotic agents[12]. In contrast, loose binding agents, which are more easily displaceable by endogenous dopamine, seem to preserve well-being even at higher occupancy levels[13]. There is some evidence that partial agonist antipsychotics, which are expected to lead to agonistic dopamine activity, are also beneficial for patients subjective well-being[14]. Mizrahi et al.[14] found a significant improvement in subjective well-being (measured with the SWN) after switching (from no antipsychotic medication, risperidone, olanzapine, or clozapine) to aripiprazole. Concluding, despite aripiprazole's high D_2-receptor affinity (2 nM), the fact that it is a partial agonist it is expected that the "netto" dopaminergic neurotransmission is relatively preserved, resulting in its favourable subjective well-being profile, comparable to looser binding agents[14].

In contrast to the above-mentioned findings, other studies found no significant differences in subjective well-being (measured with the SWN) between antipsychotic agents[15–17]. One study[18] found a favourable effect for olanzapine on subjective well-being compared to both risperidone and clozapine. This result is explained by the authors because of possible beneficial effect of olanzapine on cognition, increasing well-being[19,20].

The inconsistent results of above-mentioned studies ask for more clarification. Therefore, the primary aim of the current study is to explore the relation between the estimated dopamine D_2-receptor affinity and subjective well-being within a large sample of patients with psychotic disorders using different antipsychotic agents. We hypothesize that patients using antipsychotics with lower D_2-receptor affinity as well as partial agonistic binding agents will report higher levels of subjective well-being compared to those using a tighter binding antip-

sychotic agents. Subsequently, we hypothesize that the subjective well-being of patients who switched to 'looser' binding agents will show more improvement over time compared to patients who changed to 'tighter' binding antipsychotics.

Methods

Data from the Genetic Risk and Outcome of Psychosis (GROUP) (official release 4.0) study was used[21]. The GROUP study is a multi-center, longitudinal (follow up after three and six years) cohort study, studying genetic and non-genetic vulnerability and resilience factors for variation in the expression of psychotic disorders[21]. The GROUP-project is a collaboration of four university departments of psychiatry in the Netherlands (Amsterdam, Groningen, Maastricht, and Utrecht), and data was gathered in thirty-six involved institutes[21]. The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and subsequently by local review boards of each participating institute[21]. Patients were recruited in the Netherlands and Dutch speaking parts of Belgium, by screening case-loads and approaching candidates[21]. All patients were given detailed information on the study and informed consent was obtained.

Subjects

At baseline, 1120 patients were included in the GROUP study, as well as 1057 siblings, 919 parents and 590 healthy controls. Here we report on patients participating at baseline and 3-year follow-up assessments.

The inclusion criteria of the patients sample were:

1. Age from 16-50;
2. Diagnosed with a psychotic disorder (as described in DSM-IV TR, American Psychiatric Association, 2000), based on interviews using Comprehensive Assessment of Symptoms and History (CASH)[22] or Schedules for Clinical Assessment in Neuropsychiatry (SCAN) version 2.1[23];
3. Good command of the Dutch language;
4. Being able and willing to provide written informed consent[21].

For the current study, patients were excluded if:

1. Patients were prescribed more than one antipsychotic agent at time of assessment;
2. Patients were not prescribed antipsychotic medication at time of assessment;
3. Type of prescribed antipsychotic medication was unknown;
4. In case the SWN was not administered. Also, data of Maastricht University could not be included in the current study because the SWN was not administered at this site.

Measures

Subjective well-being. Subjective well-being was assessed with the SWN: Subjective Well-being under Neuroleptics scale (Naber, 1995); short form (SWN-K). In this 20-item self-rating scale, patients rank statements on their subjective well-being during the last week, for instance: 'I feel very comfortable in my body', on a six-point likert scale. The tool contains 10 positive and 10 negative statements on patients well-being. The SWN total score was found to be a reliable and valid method for measuring subjective well-being, with high internal consistency[24,25].

Medication use. The currently prescribed antipsychotic medication was assessed at baseline and 3-year follow up[21]. Prescribed antipsychotic medication was divided in three groups, based on:

1. Their estimated D_2-affinity compared to dopamine (1.5 nM) (following Seeman et al.[26]) and
2. Their function as an agonist or antagonist of dopaminergic neurotransmission (Table 1).

Table 1: Antipsychotics grouped by D2-receptor affinity compared to dopamine (1.5 nM). Ki-values are derived from the public Ki-database of the NIMH.

group	agent	affinity for the D_2-receptor
1. loose binding or partial antagonistic	quetiapine	D_2-affinity 437 nM
	clozapine	D_2-affinity 148 nM
	aripiprazole	D_2-affinity 2 nM; partial antagonism
2. moderate binding	olanzapine	D_2-affinity 31 nM
3. tight binding	haloperidol	D_2-affinity 2 nM
	perphenazine	D_2-affinity 1 nM
	lurasidone	D_2-affinity 1.6 nM
	penfluridol	comp. to haloperidol
	zuclopentixol	comp. to haloperidol
	pipamperone	comp. to haloperidol
	risperidone	D_2-affinity 4 nM
	pimozide	D_2-affinity 6 nM; comp. to haloperidol
	amisulpride	D_2-affinity 2 nM
	sulpiride	D_2-affinity 10 nM

Change of SWN scores over time after switching groups. After excluding patients with one or more of the concerned data missing, patients were divided into 'change groups', but due to small group sizes, we were not able to provide reliable results by comparing the seven change-groups. We therefore redeployed them into three larger subgroups:

1. Changing to an antipsychotic agent with a more 'loose or partial agonistic' D_2-binding (Moderate to Loose or partial agonistic + Tight to Loose or partial agonistic + Tight to Moderate (n = 40));
2. Changing to an antipsychotic agent with a more 'tight' D_2-binding (Moderate to Tight + Loose or partial agonistic to Tight + Loose or partial agonistic to Moderate, (n =10));
3. No change of D_2-binding Group (n =118).

Data analysis

Statistical Package for the Social Sciences (SPSS) 20 was used to analyse data. Patients were divided in 3 groups, according to type of medication and dopamine D_2-receptor affinity as described above. Differences in demographical data between the three groups categorized by their dopamine D_2-receptor affinity were investigated using a χ^2-test (gender), and Independent-samples t-tests groups (age, age of onset first psychosis and duration of illness). By performing an Analysis of Variance (ANOVA), SWN total scores were compared between the three categories of antipsychotics grouped by their D_2-receptor affinity. If a significant effect for group was found, Tukey Honestly Significant difference

(HSD) post-hoc analyses were conducted to reveal the nature of these differences. Additionally, regression analyses were employed to investigate whether the variation in SWN scores are predicted by the dosage of tight binding antipsychotic agents.

To test whether switching from a 'looser' D_2-receptor binding antipsychotics shows more improvement on SWN scores as compared to patients who changed to 'tighter' binding antipsychotics, a GLM repeated-measures procedure was conducted for the dependent variable (SWN scores), with group as the between-subject variable and SWN scores at baseline and follow up as within-subject variable. Effects of group and time (longitudinal dimension) as well as time by group (interaction effect) were examined.

Results

388 patients fulfilled inclusion criteria at baseline (T1). The distribution of patients in three groups based on their medication use (binding potential to the D_2-receptor) are shown in Table 2. Demographic data per group are displayed in Table 3.

Table 2: Grouping of patients based on their estimated D_2-receptor affinity at baseline

D_2-binding group	n per group/antipsychotic (%)
1. loose or partial antagonistic binding antipsychotics:	102 (26.3%)
• quetiapine	17 (4.4%)
• clozapine	52 (13.4%)
• aripiprazole	33 (8.5%)
2. moderate binding antipsychotic	136 (35%)
• olanzapine	136 (35%)
3. tight binding antipsychotics	150 (38.7%)
• risperidone	99 (25.5%)
• haloperidol	13 (3.4%)
• flupentixol	14 (3.6%)
• penfluridol	8 (2.1%)
• pimozide	7 (1.8%)
• zuclopentixol	4 (1%)
• broomperidol	1 (0.3%)
• flufenazine	1 (0.3%)
• perphenazine	1 (0.3%)
• pipamperone	1 (0.3%)
• sulpiride	1 (0.3%)

Table 3: Demographic data per antipsychotic D_2-binding group at baseline

D_2-binding group	loose or partial antagonistic (n = 102)	moderate (n = 136)	tight (n = 150)	test statistic, *p*-value
gender male/ female (no.)	83/19	114/22	117/33	$\chi^2 = 1.59$ $p = .453$
age (years)*	27.2 (6.3)	27.4 (6.8)	27.23 (7.6)	$F(2,378) = 0.04$ $p = .962$
age of onset first psychosis (years)*	21.9 (6.4)	23.7 (5.6)	23.29 (6.6)	$F(2,378) = 2.61$ $p = .750$
duration of illness (years)*	5.30 (3.2)	3.80 (4.2)	3.96 (4.7)	$F(2,378) = 4.41$ $p = .013$

* *Values are mean (SD)*

Subjective well-being and D_2-binding group.

Mean SWN scores and standard deviations for each medication group are displayed in Table 4. At both T1 ($F(2, 385) = 0.2$, $p = .804$), as well as T2 ($F(2, 287) = 0.2$, $p = .849$), there were no significant differences in SWN scores between the three groups.

Table 4: SWN total scores of patients based on the D_2-binding of their prescribed antipsychotic at baseline (T1) and follow-up (T2)

D_2-group n T1 n T2	loose 102 126	moderate 136 87	tight 150 77	total 388 290	test statistic, *p*-value
mean SWN score (SD)					
T1	81.87 (15.6)	81.58 (14.9)	82.75 (15.9)	82.11 (15.4)	$F(2,385) = 0.22$ $p = .804$
T2	87.49 (13.3)	88.36 (14.4)	87.16 (15.0)	87.66 (14.1)	$F(2,278) = 0.16$ $p = .849$

Explorative regression analyses yielded no significant associations between dosage of tight binding agents haloperidol, pimozide and risperidon with SWN scores ($r(107) = .033$, $p = .736$). Also, explorative analyses for a possible differential effect of D_2-receptor agonism showed no significant differences for aripiprazole compared to the other groups ($F(3, 384) = 0.93$, $p = .426$).

Change of SWN scores over time after switching groups.

A repeated measures ANOVA was performed with SWN sum scores as dependent variable and change group (1. No change, 2. Change to more loose binding antipsychotic agent, 3. Change to more tight binding antipsychotic agent) as the between-subject variable. There were no significant differences in demographical characteristics between the change groups in gender, age nor age of onset. Means, standard deviations and SWN change scores are presented in Table 5. A small to moderate significant interaction effect between 'change group' and time was found, Wilks' Lambda = 0.962, $F(2,165) = 3.254$, $p = 0.041$, partial $\eta^2 = 0.038$. Thus, the course of SWN scores differed between the groups. Also, there was a statistically significant main effect for time, Wilks' Lambda = 0.861, $F(1,165) = 26.673$, $p < 0.000$, partial $\eta^2 = 0.139$. However, hoc tests yielded no significant changes in SWN scores between the groups (Tukey HSD, $p > 0.05$). Because of the small and unequal group sizes, these results should be interpreted with caution.

Table 5: Descriptives of SWN sum scores at T1 and T2 and change scores for each change group

group, n	mean SWN score T1 (SD)	mean SWN score T2 (SD)	mean SWN change
no change of group, 118	81.5 (15.9)	86.2 (14.0)	+ 4.7
changed to more loose or partial antagonistic binding antipsychotic, 40	85.9 (14.8)	91.4 (11.6)	+ 4.5
changed to more tight binding antipsychotic, 10	71.4 (19.6)	88.0 (13.8)	+ 16.6

To exclude the possibility that switching to a specific 'loose or partial agonistic' binding agent would yield significant differences in SWN scores compared to the others, explorative analyses on specific changes from a tighter binding group to one of the individual 'loose or partial agonistic' agents were performed. This did not yield significant differences.

Discussion

This study aimed to assess differences in subjective well-being (SWB) between antipsychotic agents, grouped by their affinity for the dopamine D_2-receptor. In contrast to our expectations, we found no significant differences in SWN scores between groups of patients using estimated tight, moderate or loose binding antipsychotics at baseline or follow up. Also, we did not find more improvement in SWB in patients who switched to looser D_2-receptor binding antipsychotics as compared to patients who changed to tighter binding agents.

Several factors may explain this absence of a clear relationship between D_2-receptor affinity and subjective well-being. First, the average duration of illness was longer (although not significant) for patients in the 'loose binding group' as compared to the other two groups. This is probably mainly related to the large proportion of clozapine users (50% of the participants), who had a longer period of illness (data not shown). Patients treated with clozapine are often non-responders to two (or more) different antipsychotics, since clozapine is mainly prescribed for treatment resistant schizophrenia due to its side effects[1,27]. It may be that this subgroup of patients represents a group with more serious illness characteristics; these illness characteristics may impact on SWB. Second, we did not account for the duration of antipsychotic agent usage since we assessed at only two moments and precise information about the duration of usage was unknown. However Vothknecht and colleagues found that subjective well-being increases over time in patients with all types of antipsychotic treatment[28]; a finding that was replicated in our study. Although Mizrahi et al.[14] found a sustained amelioration of SWN after 6 months of using aripiprazole, the most substantial amelioration took place after the first week of usage[14]. Possibly, the positive impact of treatment of antipsychotic symptoms increases, or the negative impact of antipsychotic treatment decreases, with time.

Third, the one study that did find differences in well-being (defined as positive and negative affect) between patients using tight or loose binders[13], used a method (the Experience Sampling Method) that is more ecologically valid and more sensitive to the affective changes caused by D_2-receptor blockage than the SWN, because it is registered multiple times a day in the daily life of a patient. The SWN may not be sensitive enough to replicate findings concerning positive and negative affect in daily life since it focusses on other factors (physical and motoric) as well. Otherwise, when assessed on the long term, findings concerning positive and negative affect might be overruled by amelioration or deterioration on other domains of the SWN. For example, patients might get used to

physical side effects, such as drowsiness by olanzapine and a changed sleeping pattern with aripiprazole, and score higher on the physical sub-domains of the SWN.

Fourth, even though our participants, having agreed to cooperate in a study, are relatively compliant patients, we have no distinctive information on medication compliance. We might have been estimating a high dopamine D_2-receptor occupancy in the tight binding group, where in reality there could be a lower actual receptor occupancy in tight binding agents due to non-adherence. Fifth, by comparing antipsychotic medication by estimated dopamine D_2-affinity we disregarded the differential influence of antipsychotics on other neurotransmitter systems. For instance, the anticholinergic side effects (such as drowsiness, sedation) induced by clozapine may have had an unfavourable impact on subjective well-being. Also, weight gain and metabolic side effects associated with clozapine and olanzapine or aripiprazole-induced akathisia may have lowered subjective well-being in the loose binding or partial agonistic group. Nevertheless, our findings are in line with other studies reporting no significant differences in SWN scores between antipsychotic agents suggesting that a distinction between loose and tight binders is not valid concerning subjective well-being[15–17].

We also could not confirm our hypothesis that the subjective well-being of patients who switch to 'looser' binding agents shows more improvement as compared to patients who changed to 'tighter' binding antipsychotics. On the contrary, switching from a loose to a tight binding group was associated with an increase in subjective well-being. Subjective well-being may however be influenced by other subjectively unpleasant symptoms that cause patients wanting a switch to another antipsychotic agent, such as sedation. This might be an explanation for the — non-significant — increase in SWN scores in the "changing to a tight binder" group.

Taken together, we have not been able to find further support for the hypothesis that subjective well-being is associated with affinity, nor partial agonistic binding, to the dopamine D_2-receptor by antipsychotic medication in a large naturalistic study. This might imply that the clinical effect of loose binding antipsychotics on subjective well-being is not large enough to be detected in a naturalistic study. Other factors besides dopamine antagonism are probably very relevant for subjective well-being. Our results do not reject the possibility that individual differences in susceptibility for subjective unwell-being by certain antipsychotic medication remain clinically relevant.

Acknowledgments

Genetic Risk and Outcome of Psychosis (GROUP) investigators: Richard Bruggeman *(University Medical Center Groningen, Department of Psychiatry, University of Groningen, The Netherlands)*, Wiepke Cahn *(University Medical Center Utrecht, Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, The Netherlands)*, Lieuwe de Haan *(Early Psychosis Department, Amsterdam Medical Center, Department of Psychiatry, Amsterdam, The Netherlands)*, René S. Kahn *(University Medical Center Utrecht, Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, The Netherlands)*, Carin J. Meijer *(Early Psychosis Department, Amsterdam Medical Center, Department of Psychiatry, Amsterdam, The Netherlands)*, Inez Myin-Germeys *(Maastricht University Medical Centre, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht, The Netherlands)*, Jim van Os *(Maastricht University Medical Centre, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht, The Netherlands; University Medical Center Groningen, Department of Psychiatry, University of Groningen, The Netherlands)* and Durk Wiersma *(University Medical Center Groningen, Department of Psychiatry, University of Groningen, The Netherlands)*.

The authors are grateful for the generosity of time and effort by the patients and their families, healthy participants, and all the researchers who made this GROUP project possible. The infrastructure for the GROUP study is funded through the Geestkracht program of the Dutch Health Research Council (ZON-MW, grant number 10-000-1001) and matching funds from participating pharmaceutical companies (Lundbeck, AstraZeneca, Eli Lilly, Janssen-Cilag) and universities and mental healthcare organizations [Amsterdam: Academic Psychiatric Centre of the Academic Medical Center and the mental health institutions: GGZ Ingeest, Arkin, Dijk en Duin, GGZ Rivierduinen, Erasmus Medical Centre, GGZ Noord Holland Noord. Maastricht: Maastricht University Medical Centre and the mental health institutions: GGZ Eindhoven en de kempen, GGZ Breburg, GGZ Oost-Brabant, Vincent van Gogh voor Geestelijke Gezondheid, Mondriaan Zorggroep, Prins Clauscentrum Sittard, RIAGG Roermond, Universitair Centrum Sint-Jozef Kortenberg, CAPRI University of Antwerp, PC Ziekeren Sint-Truiden, PZ Sancta Maria Sint-Truiden, GGZ Overpelt, OPZ Rekem. Groningen: University Medical Center Groningen and the mental health institutions: Lentis, GGZ Friesland, GGZ Drenthe, Dimence, Mediant, GGNet Warnsveld, Yulius Dordrecht and Parnassia psycho-medical center (The Hague). Utrecht: University Medical Center Utrecht and the mental health institutions Altrecht, GGZ Centraal, Riagg Amersfoort and Delta]. Prof. de Haan received a ZON-MW grant of the Dutch Ministry of Public Health for the construction and implementation of the Personal Antipsychotic Choice Index. The current study was achieved as an additional project within this budget.

Conflicts of interests

Prof. de Haan has received an investigator-initiated grant from Eli Lilly (>36 months ago) and was a member of speakers/advisory boards for Eli Lilly, Janssen-Cilag, and AstraZeneca. For the remaining authors there are no conflicts of interest.

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CHAPTER 4

Subjective well-being (SWB) is associated with treatment adherence and symptom outcome in people with psychotic disorders. Also, it is associated with psychosis susceptibility and it is partly heriditary. The SWN-20 is a widely used tool to assess subjective well-being in patients; it was also found to be suitable for assessing SWB in healthy populations. Yet it is unclear how this retrospectively measured construct may be associated with momentary affective state, which is the proposed underlying mechanism of subjective well-being. This study therefore investigated the ecological validity of the SWN-20 in people at different risk for psychosis. In 63 patients with a psychotic disorder and 61 siblings of patients with a psychotic disorder we assessed whether subjective well-being as measured with the SWN-20, was associated with momentary positive affect, negative affect, reward experience and stress-sensitivity as measured by the experience sample method (ESM). Higher subjective well-being was associated with higher momentary positive affect and lower negative affect, and this association was not conditional on psychosis vulnerability. Subjective well-being was not associated with stress-sensitivity or reward-experience. SWN-20 is an easy-to-use and ecologically valid tool to measure subjective well-being in people with different vulnerability for psychosis.

AN EXPERIENCE SAMPLING STUDY ON THE ECOLOGICAL VALIDITY OF THE SWN-20: INDICATION THAT SUBJECTIVE WELL-BEING IS ASSOCIATED WITH MOMENTARY AFFECTIVE STATES ABOVE AND BEYOND PSYCHOSIS SUSCEPTIBILITY

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IN: PSYCHIATRY RESEARCH, 258 (2016), 1-5

Introduction

During the last decades, research in psychology has seen a shift to a more resilience-based approach including focussing on subjective well-being (SWB)[1]. However, research still suffers from low consensus on the definition of SWB. According to Diener[2], SWB is a multifaceted cognitive-affective construct encompassing high positive affect, low negative affect and more satisfaction with life, the latter representing the cognitive component. This broadly defined SWB is associated with better health and longevity in the healthy population[3]. Within the research of psychosis, SWB is frequently measured by a questionnaire that was originally developed to assess well-being under the use of neuroleptics, the Subjective Well-being under Neuroleptic Treatment (SWN)[4]. Compared to healthy people, this narrowly defined SWB is found to be lower in people with schizophrenia and is related to treatment adherence and symptom outcome in this population[5]. The SWN measures five subscales: emotional regulation, self-control, mental functioning, social integration and physical functioning. These domains are sensitive to neuroleptics, but lower scores are not specific to schizophrenia patients: a shortened version of the original SWN, the SWN-20[4,6] proved to be reliable in measuring SWB in relative of schizophrenia patients and healthy controls, and lower scores on the subscales correlated with sub-clinical psychotic symptoms in healthy controls and siblings[7]. In line, individuals with schizotypal traits experience diminished SWB[8,9], and SWB is found to be for 40-50% heritable[10]. This is indicative for a trait feature of lower well-being across the psychosis continuum. Taken together, trait SWB seems to be associated with a psychosis susceptibility, as well as with outcome. This notion makes further studies on families that are at higher risk for developing psychosis relevant. Especially, including siblings of patients with psychotic disorders enables us to distinguish illness-related factors from familial liability to psychosis, and the SWN-20 may serve as a reliable measure of SWB across the psychosis-spectrum. As SWB is sensitive-, but also non-specific- to neuroleptic use, as indicated by lower SWB across the psychosis spectrum, other targets for treating low SWB may be investigated. Fredrickson[11] argues in the 'broaden-and-build theory of positive emotions', that especially momentary positive affect may enable a person to build up personal and social resources, thereby strengthening support and increasing SWB. It is also proposed that 'reward experience'- or the tendency to experience momentary positive affect in relation to positive environmental experiences may aid well-being[12,13]. Reversely, stress-sensitivity, - or experienced negative affect following stressful events-, is found to be a risk-factor

both for depression[14] and for psychosis[15–19] and may be associated with SWB. As Menne-Lothman et al. demonstrate[13], reward experience and stress-sensitivity both represent discrete phenotypes. Also, tentative evidence suggests they are influenced by genetic factors[18,20–22]. Studying the SWN-20 in relation to momentary affective states is relevant from a theoretical perspective, as momentary affective states are hypothesized as underlying mechanisms of subjective well-being. However, their relationship has not been studied so far. It is also clinically relevant as this topic may provide a hint for targets in therapy: e.g. if scores on SWB according to the SWN-20 correlate with momentary affective states, targeting affect in treatment may benefit overall SWB, which may in turn impact on better outcome or improved treatment adherence in patients. One method that has been used to capture momentary affect is experience sampling (ESM)[23]. ESM uses subjects' self-reports on positive and on negative affect and symptoms at several random moments during the day. This enables measurement of moment-to-moment associations between daily life context and affect or symptoms as well as fluctuations of affect or symptoms without confounding of recall bias[24].

The aim of our study is to investigate the ecological validity of the SWN-20 in people with different vulnerability for psychosis, i.e. patients with a psychotic disorder, siblings of patients with psychotic disorders and healthy controls whilst controlling for antipsychotic medication use in patients as antipsychotic medication that are stratified by their binding potential to the dopamine D_2-receptor are differentially associated with momentary affect[25] as well as with SWB[26–28]. We hypothesize that SWB is associated with positive affect and negative affect, and with reward experience and stress-sensitivity as assessed with ESM, irrespective of genetic vulnerability status groups, indicating ecological validity across the psychosis spectrum.

Methods

2.1 Study design

The present study concerned data from the Genetic Risk and Outcome of Psychosis (GROUP) research project, a naturalistic, longitudinal cohort study[29] carried out in patient samples, their siblings, and healthy controls. For this study, we used a sub-sample of data collected at wave three concerning patients and siblings. Participants were included if they completed experience sampling as well the SWN-20 questionnaire at wave three. The study protocol was approved by the Ethical Review Board of the University Medical Centre Utrecht.

2.2 Sample

For this study, data were gathered by mental health institutes affiliated to the Amsterdam and Groningen sites. Siblings were recruited through their ill relatives. The Comprehensive Assessment of Symptoms and History[30] was completed by trained psychologists or psychiatrists to assess symptom history, yielding disorder diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition[31] criteria that were cross-referenced with clinicians involved with the subjects. Baseline inclusion criteria for the GROUP study were:

a. age between 16 and 50 years;
b. good command of the Dutch language;
c. being able and willing to give written informed consent after given the opportunity to think about participation.

Inclusion criteria for patients were:

d. a diagnosis of psychotic disorder.

Exclusion criterion for siblings was a life time history of psychotic disorder.

All potential patients who declined to participate or otherwise did not participate were eligible for treatment (if applicable) and were not disadvantaged in any way in case of non-participation. A total of 63 patients (70.8%) and 61 siblings (80.3%) completed more than 20 entries on the ESM and were therefore included in our study, in line with Palmier-Claus et al.[24]. The mean of entries for patients was 39 (SD 22.6) and for siblings 37.4 (SD 10.7). Of the 63 patients, 35 were diagnosed with schizophrenia; 11 with a psychotic disorder NOS; 8 with a schizoaffective disorder; and 8 with a psychosis spectrum disorder. See Table 1 for demographic and clinical variables. As this study concerns wave three of a naturalistic longitudinal study, our sample was subjected to attrition. This is detrimental for detecting effects between the status groups, especially concerning Level 2 data. Yet, power on the ESM data on Level 1 was high, with more than 60 participants per status group with a minimum of 20 data-entries[32] ensuring that we were likely to find some effect if associations between the status groups would differ. Yet, concerning stress-sensitivity and reward experience, which were reduced to Level 2 data, power of this sample proved to be 0.60 with effect size 0.2.

2.3 Clinical measures

SWB was assessed by using the SWN-20[4,6]. This 20-item self-rating scale contains 10 positive and 10 negative statements on patients well-being, on a six-point Likert scale. Higher scores indicate higher SWB. Subjects rank statements on their subjective well-being in the last week, for instance: 'I feel very comfortable in my body'. The SWN-20 is a reliable and valid method for measuring subjective well-being, with high internal consistency[7]. We used adjusted mean score on all items so as to account for missing values.

2.3.2. Positive affect, negative affect, reward experience and stress-sensitivity

ESM was conducted using a 'Psymate', or palmtop[33] with a 52 item, 7-point Likert scale questionnaire regarding appraisal of daily life events, items on different mood symptoms, self-esteem, hallucinations, disorganization, paranoid ideation and social context at the present moment. Ten times a day on six consecutive days, the Psymate emitted a signal at random moments between 7:30 a.m. and 10:30 p.m., after which patients filled in the questionnaires. For this study the following (higher order) variables were used: negative affect (mean score on items: insecure, down, lonely, anxious, irritated), and positive affect (cheerful, satisfied, relaxed, enthusiastic). To measure reward experience, positive affect was regressed on events rated as pleasant, resulting in a separate coefficient for each individual whilst accounting for shared variance in repeated measures[13]. Stress-sensitivity was defined as the coefficient of negative affect following negative appraised events 19. Cronbach's alpha for the negative affect scale (Level 2) proved to be $\alpha = 0.86$ for patients and $\alpha = 0.9$ for siblings. For the positive affect scale it proved to be $\alpha = 0.94$ for patients and $\alpha = 0.93$ for siblings.

2.3.3. Medication status

We divided antipsychotic medication according to their affinity to the dopamine D_2-receptor, as well as their function as an agonist or antagonist of dopaminergic neurotransmission, a method also used by de Wit et al.[34] (table1). If subjects used two antipsychotic agents simultaneously, the tighter binding group was used as default.

Table 1: Antipsychotics grouped by their D_2-receptor affinity compared to dopamine

group	agent
loose binding	quetiapine clozapine aripiprazole [partial agonist/antagonist
moderate binding	olanzapine
tight binding	haloperidol perphenazine lurasidone penfluridol zuclopentixol pipamperone risperidone pimozide flupentixol amisulpride sulpiride

Division based on de Wit et al.[34]

2.4. Statistical analyses

For analyses, IBM SPSS Statistics version 22 was used. As ESM data has a hierarchical structure with observations nested within subjects, and subjects within families, (generalized) linear mixed models were carried out. The Genlinmixed command in SPSS allows for skewed or dichotomous outcome measures as well as for dependency in nested data. Analyses were conducted after we determined which distribution and link function would fit the data the best. Concerning momentary negative and positive affect, data gathered per beep were assumed to be correlated with adjacent beeps within the same person, thus model building allowed for this correlation by nesting beeps within a subject and constraining errors by an autocorrelation structure (AR1), as well as allowing observations within persons and persons within families to correlate by constraining errors with variance components (VC) in a random intercepts model. As there were no multilevel predictors, we did not estimate random slopes. Model fit was analysed by means of AIC. As reward experience and stress-sensitivity represent a single coefficient per subject, multiple regression analyses were performed on these variables. To test the hypothesis that SWB was associated with affective symptoms, reward experience and stress-sensitivity above genetic vulnerability status, we ran multiple (hierarchical) regressions and entered SWN-20 as a predictor variable and positive affect, negative affect, reward experience and stress-sensitivity as outcome variables. We entered vulnerability status, the interaction term between vulnerability status*SWN-20, sex, age and anti-psychotic use as covariates. As we ran multiple, but conservative analyses, significance was defined as $p < 0.025$.

Results

Model building indicated that a Gamma-distribution with log-link best explained the data concerning negative affect. SWN-20 significantly predicted momentary negative affect ($B = -0.37$, 95% CI [−0.52 to −0.22], F (1, 4636) = 51.8; $p < 0.001$). There was no significant interaction between vulnerability status and SWN-20 in predicting negative affect. SWN-20 predicted positive affect ($B = 0.65$, 95% CI [0.25 to 1.04], F (1, 4641) = 28.74; $p < 0.001$). The interaction between vulnerability status and SWN-20 was not significant in predicting positive affect. There were no significant associations between SWN-20 and reward experience (F (1, 114) = 3.07; $p = 0.08$), or stress-sensitivity (F (1, 98) = 0.21; $p = 0.651$), nor were these associations conditional on vulnerability status.

Table 2: Sample demographical and clinical characteristics stratified by genetic risk status

group	patients (63)	siblings (61)	controls (11)	test statistics	*p*-value
age	33.3 (7.4)	36 (8.2)	35.8 (9.5)	$F = 1.84$	0.163
non-white ethnicity	17.7%	13.6%	0%	χ^2 (2) = 2.45	0.294
marital status					
married or living together	6.5%	49.2%	27.3%	χ^2 (2) = 28.3	< 0.001
never married/single/ divorced	93.5%	50.8%	72.7%		
antipsychotic medication use					
loose binding	30.2%	-	-		
moderate binding	19%	-	-		
tight binding	19%	3.3%	-		
no antipsychotic medication	31.7%	96.7%	100%		
clinical variables					
positive affect	4.56 (0.97)	4.98 (0.69)	5.13 (0.53)	$F = 5.06$	0.008
negative affect	2.14 (0.79)	1.48 (0.51)	1.37 (0.20)	$F = 18.86$	< 0.001
reward experience	0.26 (0.24)	0.3 (0.20)	0.18 (0.15)	$F = 1.43$	0.243
stress sensitivity	0.35 (0.32)	0.25 (0.35)	0.26 (0.37)	$F = 1.12$	0.332
SWN-20 trait SWB	4.4 (0.65)	5 (0.48)	5.11 (0.41)	$F = 19.9$	< 0.001

Discussion

The aim of this study was to examine the ecological validity of the SWN-20 in patients with a psychotic disorder and their siblings. SWB was lower in patients compared with their siblings. As expected from earlier research[35], patients with psychotic disorders also experienced less positive and more negative affect than their siblings. No significant differences in reward experience between the two vulnerability groups were found, which is in concordance with earlier research showing that patients with schizophrenia express equal levels of positive affect in response to pleasant activities compared with controls[35]. Yet, there was a significant difference between the vulnerability groups in stress-sensitivity, in line with Aiello et al.[36]. Our results further show that trait SWB is associated with both momentary positive affect and momentary negative affect. Contrary to expectations, SWB was not associated with reward experience nor with stress-sensitivity. Finally, associations between SWB and momentary affective states did not differ as a function of vulnerability status, suggesting ecological validity of the SWN-20 in people with different risk for psychosis. This finding is in line with Vothknecht et al.[7] who also found evidence for validity of the SWN-20 to assess SWB across the psychosis liability spectrum. Although momentary assessment of positive and negative affect in daily life is associated with SWB measured with the SWN-20, both methods do not represent an identical construct. Earlier research for instance showed that momentary positive and negative affect differed between patients using antipsychotic agents with different affinity to the dopamine D_2-receptor[25]. This difference was not found by measuring subjective well-being with the SWN-20 in another study[34]. The fact that the SWN-20 also assesses other domains besides affect, such as physical factors, possibly explains this discrepancy, although other factors such as study design may also account for differences between the studies. The association of the SWN-20 with momentary positive and negative affect implies that the SWN-20 is a valid measurement method to assess subjective well-being retrospectively. Furthermore, the SWN-20 is efficient to use in clinical practice: it assesses SWB in only 5–10 min, total scores are easy to interpret and useful for predicting symptom reduction[37]. Although ESM is more demanding for patients compared with assessment with the SWN-20 in terms of required assessment period, it is also more sensitive for detecting subtle changes in well-being in the patient's daily life and can provide insight in SWB in both research as well as individual patients. Oorschot et al.[35] demonstrate that patients with schizophrenia experienced equal levels of positive affect in response to pleasant activities ('reward experience') compared to healthy controls, although patients experienced fewer pleasant activities, explaining the lower overall levels of positive affect. In

patients, reward experience in turn does not seem to lead to 'anticipatory pleasure' which is believed to be a motivator to behaviour; it thereby fails to increase the likelihood of pleasurable experiences in patients[38]. ESM can therefore be valuable for clinical practice: it helps to gain insight in which events induce positive affect in individual patients. Thereupon, clinicians may encourage patients to perform these activities more often, as pleasant activities are expected to enhance overall SWB. A limitation of the current study is the high between and within group heterogeneity. However, we adjusted for some of these aspects in analyses. Also, we controlled for possible confounding factors known to affect subjective well-being, such as the use of antipsychotic medication. Another important limitation is that we have not included healthy controls with low familial risk for psychosis, thereby limiting conclusions to people with a familial liability to psychosis. In conclusion, we have found evidence that SWB as assessed with the SWN-20 is associated with momentary positive and negative affect, providing us with preliminary evidence that it is an ecological valid and easy-to-use measure for both research and clinical practice.

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CHAPTER 5

One in five patients with a psychotic disorder has persistent low subjective well-being (SWB), which is associated with a poorer prognosis. In schizophrenia patients, personality traits are associated with SWB. The present study aims to evaluate whether neuroticism and extraversion influence SWB in patients with psychotic disorder and healthy controls over the course of time. In 186 patients and 126 healthy control subjects, SWB was measured with the Subjective Well-being under Neuroleptics-20 (SWN) scale at baseline, three years and six years. We used the Five-Factor Inventory to assess neuroticism and extraversion. Mixed model analyses were conducted to investigate moderating associations of positive, negative and depressive symptoms, cannabis use, illness insight, weak social support and antipsychotic medication in patients. Higher neuroticism and lower extraversion were associated with lower SWB over six years in both groups. Personality traits did not have a differential effect on the course of SWB over time. In patients, stable low SWB was found in 15.1% of subjects. This group scored highest on neuroticism and lowest on extraversion compared to subjects with an increase in SWB or a stable high SWB. Our findings underline that personality traits are correlated to subjective well-being regardless of psychotic or depressive symptoms.

A LONGITUDINAL ANALYSIS OF THE EFFECTS OF NEUROTICISM AND EXTRAVERSION ON SUBJECTIVE WELL-BEING IN PATIENTS WITH SCHIZOPHRENIA

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IN: PSYCHIATRY RESEARCH, 259 (2017), 538–544

Introduction

Subjective well-being is not only an important treatment outcome of schizophrenia, but in the past decade it has also become an undebatable part of the recovery process[1]. Subjective well-being, assessed with the Subjective Well-being under Neuroleptic treatment scale (SWN), is associated with better medication adherence[2] and early improvement of subjective well-being after starting antipsychotic medication predicts better social functioning[3–6]. Subjective well-being is lower in patients with non-affective psychotic disorders than in their family members and healthy controls[7].

Although subjective well-being is cross-sectionally associated with a range of factors, only one longitudinal evaluation of subjective well-being exists[8]. Lambert and colleagues found different clusters of subjective well-being trajectories over 12 months to 3 years[6,8].They demonstrated that one in five patients persistently experiences low subjective well-being over a period of 3 years after treatment of a psychotic episode. Thirty percent of the patients with persistently low subjective well-being showed no or only minimal improvement in symptoms and functioning[6,8]. Predictors for the stable low trajectory cluster were a low baseline SWN-score, a long duration of illness and no symptomatic and functional recovery at three months[8,9].

The studies by Lambert did not evaluate the association between personality traits and subjective well-being. A growing body of research is showing that personality traits such as neuroticism and extraversion are associated with various treatment outcomes in patients with schizophrenia, such as symptom relapse[10,11] and social functioning[11,12]. Boyette et al. found that neuroticism predicted severity of emotional distress. Extraversion was associated with lower severity of negative symptoms[12]. However, it is unknown whether these associations imply causality. Extraversion was associated with lower severity of negative symptoms[12]. Moreover, personality traits are associated with patient's subjective experiences, such as quality of life, in schizophrenia when measured cross-sectionally[13–16]. As several quality of life instruments show at least a partial overlap with the Subjective Well-being under Neuroleptics scale (reviewed by Vothknecht et al.[9]), we propose that neuroticism and extraversion are important predictors of subjective well-being and its trajectory over time.

The present study investigated subjective well-being in a sub-sample of patients and healthy controls of the Genetic Risk and Outcome of Psychosis study (GROUP-cohort), a prospective cohort study with a follow-up of 6 years. The

primary aim was to evaluate whether personality traits are associated with subjective well-being and its course. Secondary, we aimed to evaluate whether levels of neuroticism and extraversion predicted well-being trajectories. If the personality traits predict the trajectories of subjective well-being, our results would show a valuable clinical reference point for patients at risk for persistent low subjective well-being.-=======opl

Our main questions are:

1. Do personality traits predict the course of subjective well-being over three years or six years in patients with a psychotic disorder, when positive, negative and depressive symptoms are controlled for?
2. Do personality traits predict the course of subjective well-being in healthy controls, when accounted for sub-clinical depressive symptoms?
3. Do personality traits and severity of symptoms at baseline predict specific subjective well-being trajectories in patients with a psychotic disorder?

Methods

2.1 Setting and sample

The GROUP -study is a multi-center, longitudinal naturalistic cohort, designed to study vulnerability and resilience factors for variation in the expression of non-affective psychosis disorders and variation in the course of these disorders. Three academic centers (Amsterdam, Groningen and Utrecht) and their affiliated mental health care institutions provided data for the present study. For a detailed description of the study design, sampling and inclusion criteria, see Korver et al.[17].

For the current study we included 186 subjects and 126 healthy control subjects with complete data at baseline and after three years. The 6 year follow-up was attended by 85 patients (46%) and 41 controls (33%). Self-rated assessments were checked for completeness by investigators.

2.2 Measures and rating scales

Personality traits and diagnosis were assessed at baseline. All other measurements were measured at baseline and again at year 3 and 6.

We used the Subjective Well-being under Neuroleptics scale[18]; short form (SWN-K) to measure subjective well-being at each assessment. In this 20-item

self-rating scale, patients rank statements on emotional regulation, social integration, physical functioning and mental functioning during the last week on a six-point Likert scale. The scale contains 10 positive and 10 negative statements. The SWN has a high internal consistency and is the most commonly used instrument for evaluating subjective well-being in patients with psychotic disorders[7,19]. It is also validated for controls[7].

We used the self-report questionnaire of the NEO Five-Factor Inventory to measure personality traits. The NEO-FFI has shown a good construct validity and internal reliability[20,21]. We focused on neuroticism and extraversion, since these personality traits are most robustly linked to subjective well-being in healthy populations[22,23] and in patients with schizophrenia[15,16,24].

The Positive and Negative Syndrome Scale (PANSS) was used to evaluate symptom domains at all assessments[25]. The PANSS consists of three subscales: a positive syndrome scale (items P1–P7), a negative syndrome scale (items N1–N7), and a general psychopathology scale (items G1–G16). Van der Gaag et al. however developed the best fitting factor model, consisting of five factors (positive symptoms, negative symptoms, disorganization, excitement and emotional distress)[26]. We have taken the positive and negative symptoms from this 5-factor model. Depressive symptoms were assessed using the emotional distress subscale.

For cognitive function, we used the digit symbol substitution scale of the Wechsler Adult Intelligence Scale as a measure for thought processing speed[27]. Since the SWN was originally introduced as a way to assess experiences under treatment with antipsychotic medication[18], we have corrected for current antipsychotic medication use (yes/no). Moreover, we assessed the following variables as possible confounders. Current cannabis use (yes/no) was investigated using the Composite International Diagnostic Interview (CIDI,[28]), of which the Substance Abuse Module covers cannabis use. Ethnicity was included for illustration of the background of the sample, as having a migration background is a risk factor for psychosis[29]. The influence of negative social support was assessed with the Sociale Steunlijst-Negatief (Social Support – Negative, [30]). For illness insight, we used the Birchwood Insight Scale[31]. Furthermore, extrapyramidal symptoms were assessed with the Barnes Akathisia Rating scale[32], the United Parkinson Disease Rating Scale[33] and the Abnormal Involuntary Movement rating Scale[34].

2.3 Data analysis

SPSS 23 was used for all analyses. We used GROUP database version 5.0. Sample characteristics between patients and controls were compared with *t*-tests (continuous data) and χ^2-tests (categorical data). We carried out mixed model repeated measurements analyses with neuroticism and extraversion as predictors of subjective well-being for the period between baseline and three years and for the period between three and six years. Additionally, we added number of assessment as a factor to evaluate the effect of time on the SWN-score. Next, differential associations between the personality traits and the SWN over the course of time were assessed using interaction terms neuroticism × time and extraversion × time. Potential moderators (psychopathology, cannabis use, age, gender, duration of illness, cognitive functioning, use of antipsychotic medication, akathisia, parkinsonism, involuntary movements, illness insight, weak social support and level of education) were assessed in a separate model. The moderators that had a significant relation to subjective well-being were added together with the personality traits and number of assessment en bloc in a final model.

The commonly used criteria for response in clinical trials are defined by a SWN-K-score of > 80 and an improvement of at least 20% and at least 10 points[9]. We investigated SWN-changes as follows: we dichotomized the sample according to a baseline SWN-score below < 80 ('low') or ≥ 80 ('high'). An SWN-change score was calculated by subtracting the follow-up assessments from the baseline score. We defined a clinically relevant change score as at least 20% and at least 10 points change from the former assessment and a stable score when there was less than 20% or 10 points change from the former score. Subjects with a low baseline SWN-score and no clinical relevant improvement over 3 or 6 years were assigned to the 'stable low'-trajectory. A 'low start, improving'-trajectory was defined when, after a low baseline SWN-score, subjects had an improvement at 3 years or at 6 years. The third group of interest was the 'stable high'-trajectory group, consisting of subjects with a high SWN-score at baseline that stayed within a 20% or 10 points change over at least 3 years.

We assessed differences in neuroticism, extraversion, positive, negative and depressive symptoms at baseline across the three trajectory groups by using an explorative analysis of variance (MANOVA). Least Significant Different post-hoc comparisons were performed to assess specific differences between the groups. We used effect size Cohen's *d* to investigate the individual contribution of the separate personality traits and psychopathological symptoms to a well-being trajectory.

Results

3.1 Sample demographics

On average, patients had a lower SWN-score than controls, were more often of male gender, had a lower total IQ and cognitive functioning and used less often cannabis than healthy controls (see Table 1.).

Table 1: Baseline socio-demographic and clinical characteristics of the sample.

		patients, n = 186 mean (SD), n(%)	controls, n = 126 mean (SD), n(%)
age		28 (7)	28 (10)
gender	male	153 (82.2)	72 (57.1)†
	female	33 (17.7)	54 (42.9)†
ethnicity	causasian	146 (78.5)	108 (85.7)
	moroccan	5 (2.7)	1 (0.8)
	surinamese	4 (2.2)	1 (0.8)
	turkish	3 (1.6)	0 (0)
	other	3 (1.6)	1 (0.8)
	mixed	20 (10.7)	11 (8.7)
	not recorded	5 (2.7)	4 (3.2)
diagnosis (n)	schizophrenia	151 (81.2)	-
	schizophreniform disorder	2 (1.1)	-
	schizoaffective disorder	27 (14.5)	-
	other psychotic disorder	6 (3.2)	-
number of psychotic episodes		2 (1)	-
duration of illness in years		4.5 (4.6)	-
WAIS total IQ		95 (16)	109 (15)†
WAIS digit symbol substitution scaled score		7 (3)	11 (3)†
any cannabis use past 12 months			
	yes	125 (67.2)	101 (80.2)†
	no	60 (32.3)	22 (17.4)†
	unknown	1 (0.5)	3 (2.4)†
current use of antipsychotics			
	currently using	173 (93.0)	-
	not currently using	10 (5.4)	-
	unknown	3 (1.6)	-
PANSS	positive symptoms	13 (6)	-
	negative symptoms	16 (6)	-
	emotional distress	15 (5)	-
CAPE	positive symptoms	-	0.18 (19)
	negative symptoms	-	0.43 (28)
	emotional distress	-	0.52 (29)
NEO-FFI	neuroticism	36 (9)	27 (6)†
	extraversion	37 (7)	44 (6)†
SWN total score	initial	82.18 (16.94)	102.40 (8.22)†
	3 years	87.03 (13.82)	102.33 (9.18)†
	6 years	87.03 (13.06)[a]	102.78 (9.34)[b,†]

a: subsample of patients, n = 85. b: subsample of controls, n = 41. †: mean difference for $p < 0.01$

3.1 Predictive value of neuroticism and extraversion on subjective well-being over the first three years

3.1.1 Patients

Mixed model analyses showed an uncorrected significant negative association of neuroticism with subjective well-being (t = -6.67, $p < 0.001$), a positive association of extraversion (t = 5.90, $p < 0.001$) and a positive association of time (t = 3.93, $p < 0.001$). No significant associations were found for the interaction terms neuroticism × time and extraversion × time. Age, duration of illness, cognitive function, highest level of education, antipsychotic medication use, parkinsonism and akathisia had no significant effect on SWN-score. Positive symptoms had a positive effect on SWN t = 2.27, p = 0.024. Female gender, cannabis use, negative symptoms, emotional distress, illness insight and weak social support had a negative effect on SWN-score, t = -2.05, p = 0.042; t = -3.16, p = 0.002; t = 3.42, p = 0.002; t = -6.07, $p < 0.001$; t = -4.90, $p < 0.001$; t = -6.14, $p < 0.001$. After adding significant moderators to the model, the effects of neuroticism and extraversion remained (t = - 3.07 and t = 4.34, for $p < 0.05$), see table 2. Time was not significantly associated with SWN.

Comparisons of those who dropped out for third assessment to those with complete data showed no significant differences regarding personality scores, diagnoses, psychopathology, cannabis use intensity and weak social support at the second assessment. Levels of insight were lower in those who remained in the study (mean difference 1.23, p = 0.007).

Table 2: Mixed model repeated measurement results of the effect of neuroticism, extraversion and the course of time between baseline and 3 years on subjective well-being. Associations are corrected for gender, cannabis use, positive symptoms, negative symptoms, emotional distress, illness insight and weak social support.

	patients					controls			
parameter	est.	SE	t	sig.	parameter	est.	SE	t	sig.
intercept	109.13	7.92	13.79	0.000	intercept	110.42	6.11	18.08	0.000
neuroticism	-0.30	.098	-3.07	0.002	neuroticism	-0.63	0.11	-5.96	0.000
extraversion	0.50	0.12	4.34	0.000	extraversion	0.27	0.10	2.66	0.009
time	1.59	1.42	1.12	0.265	time	-0.13	0.80	-.017	0.869

3.1.2 Controls

Mixed model analyses showed an uncorrected significant negative effect of neuroticism on subjective well-being (t = -8.86, $p < 0.001$), a positive effect of extraversion (t = 5.90, $p < 0.001$) and a positive effect of time (t = 3.15, $p = 0.002$). No interaction effect of time and personality traits was found. Age, gender, cognitive function, cannabis use, level of education and the frequency of positive sub-clinical positive symptoms were not associated with the SWN-score. The frequency of depressive and negative symptoms had a negative relation with the SWN (t = -2.03, $p = 0.04$ and t = -4.17, $p < 0.001$).

After correction for depressive and negative symptoms in the final model, the effects of neuroticism and extraversion remained significant (t = -6.00, $p \leq 0.001$ and t = 2.66, $p = 0.009$). Subgroup analysis of the lost-to-follow up sample compared to those who participated in the third assessment, showed no significant differences on personality scores, cannabis use intensity, negative and depressive symptom scores at the second assessment.

3.2 Predictive value of baseline neuroticism and extraversion on subjective well-being at year three to six

3.2.1 Patients

In the three to six years after initial assessment, we found a negative effect of neuroticism on subjective well-being, t = -2.58, $p = 0.012$ and a positive effect of extraversion, t = 3.41, $p = 0.002$. We found no significant time effect. We found no significant association for the interaction terms neuroticism × time or extraversion × time or for positive symptoms, age, gender, duration of illness, level of education, cannabis use, use of antipsychotic medication or akathisia on SWN-score. Cannabis use, illness insight, weak social support and negative and depressive symptoms however, were negatively associated with the SWN score (t = -2.97, $p = 0.003$; t = -4.95 $p < 0.001$; t = -4.80, $p < 0.001$; t = -3.93, $p < 0.001$; t = 4.40, $p < 0.001$). After correction for these covariates in the final model, the effect of neuroticism and extraversion remained significant (t = -2.62, $p = 0.009$ and t = 3.51, $p = 0.001$), see table 3.

Analysis of the third assessment drop outs, showed no difference on personality scores, baseline diagnoses, cannabis use intensity, weak social support and negative and depressive symptom scores at the second assessment. Levels of insight were lower in those that remained in the study (mean difference 1.23, p = 0.007).

Table 3: Mixed model repeated measurement results of the effect of neuroticism, extraversion and the course of time between 3 and 6 years on subjective well-being. Associations are corrected for gender, cannabis use, positive symptoms, negative symptoms, emotional distress, illness insight and weak social support.

	patients					controls			
parameter	est.	SE	t	sig.	parameter	est.	SE	t	sig.
intercept	113.83	8.92	12.75	0.000	intercept	109.37	6.51	16.79	0.000
neuroticism	-0.30	0.11	-2.63	0.009	neuroticism	-0.42	0.11	-4.20	0.000
extraversion	0.47	0.13	3.51	0.001	extraversion	0.27	0.10	2.68	0.008
time	red.				time	-0.47	1.12	-0.42	0.678

3.2.2 Controls

We again found an uncorrected negative association of neuroticism and a positive association of extraversion with subjective well-being over the three to six year follow-up period, $t = -7.69$, $p < 0.001$ and $t = 3.28$, $p = 0.001$. No association with the SWN was found for the interaction of time and personality traits, nor for sub-clinical positive symptoms, gender, cognitive function, cannabis use, level of education. Depressive and negative symptoms were significantly related to the SWN ($t = -2.50$, $p = 0.013$; $t = -5.51$, $p < 0.001$), as was age in this time frame ($t = -2.44$, $p = 0.017$). After correction, neuroticism and extraversion remained significantly associated with subjective well-being. Time remained unassociated.

3.3 Assessment of different SWN trajectories over the course of 6 years

3.3.1 Patients

We found 28 patients with a stable low SWN-trajectory (15.1% of our sample). A larger subgroup of 55 patients (29.6%) had a low start and improving SWN-development. This group had a low SWN-score at baseline but reached an amelioration in SWN-score over 3 years and over 6 years, or over 6 six years only. We found 84 patients (45.2%) having a stable high SWN over three or 6 years. Another 19 patients (10.2%) had strongly changing SWN-scores over the assessments. See also figure 1 for the resulting three trajectory groups. We excluded the heterogeneous group from our analyses, considering our focus on discerning the predictors of the patients that have a stable low subjective well-being trajectory.

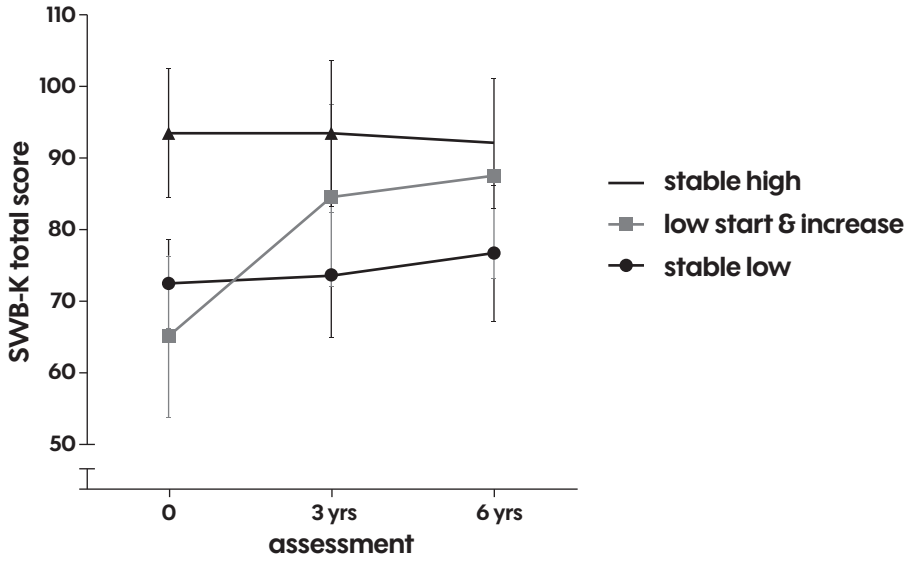

Figure 1: Average course of subjective well-being in different trajectories.

Using Wilk's lambda, we showed an overall group difference on neuroticism, extraversion, positive -, negative - and depressive symptoms, F (10, 143), $p <$ 0.001. Subsequent post-hoc pairwise comparisons demonstrated that the 'stable low'-trajectory differed significantly on neuroticism from the 'low start and improving'-trajectory (mean difference (MD) 4.25, $p = 0.03$) and on neuroticism (MD 10.75, $p < 0.001$), extraversion (MD -7.66, $p < 0.001$) and emotional distress (MD 3.34, $p = 0.005$) from the 'stable high'-trajectory. The 'low start and improving'-trajectory differed from the 'stable high'-trajectory on neuroticism (MD 6.50, $p < 0.001$), extraversion (MD -4.95, $p < 0.001$), positive symptoms (MD 2.92, $p = 0.013$), negative symptoms (3.04, $p = 0.006$) and depressive symptoms (MD 3.70, $p < 0.001$). Effect sizes are shown in table 4.

3.3.2. Controls

We found that 119 (94.4%) of healthy control subjects belonged to the 'stable high'-SWN trajectory. No 'stable low' trajectories existed in the control group. The 'low start and improving'-group consisted of 2 (1.6%) subjects and 5 (4.0) fell in the 'other trajectory'-group. The small numbers in these last two groups precludes comparison between groups.

Table 4: Comparison of personality traits and symptoms at baseline between three trajectory groups in patients.

	stable low vs low start,improving			stable low vs stable high	
variables at baseline	low start, improving mean (SE)	Cohen's *d*	stable low mean (SD)	Cohen's *d*	stable high mean (SE)
neuroticism	38.4 (8.3)	0.58	42.7 (4.9)	1.59	31.9 (7.7)
extraversion	34.8 (7.4)	0.44	31.1 (6.1)	1.38	39.8 (5.9)
positive symptoms	15.1 (6.9)	0.19	13.8 (7.1)	0.13	12.2 (5.9)
negative symptoms	17.6 (6.0)	0.07	17.4 (7.4)	0.39	14.6 (5.7)
emotional distress	17.2 (5.9)	0.04	16.9 (4.7)	0.73	13.5 (4.1)

Discussion

The aim of the present study was to increase our understanding of the effect of personality traits on the course of subjective well-being in patients with schizophrenia and healthy controls. For both groups, we found that neuroticism is negatively associated and extraversion is positively associated with subjective well-being over three years, extending to six years. The personality traits do not have a differential effect on the course over time. However, patients with a stable low subjective well-being over 3 or 6 years had a higher score on neuroticism and a lower extraversion score with moderate effect sizes compared to patients that showed an increase in subjective well-being. Compared to patients with a stable high subjective well-being trajectory, effect sizes of high neuroticism and low extraversion were larger. Subjective well-being in patients with schizophrenia is not only associated to disorder-specific state factors such as positive, negative and depressive symptoms or treatment, but is also independently associated with trait factors in the form of personality traits as measured by the Five Factor Model.

The present study comprises the longest follow-up of subjective well-being in patients with non-affective psychotic disorders to date. Earlier studies showed that a higher degree of neuroticism and a lower degree of extraversion are cross-sectionally associated to quality of life[14,16,35]. Our results show that this association remains stable over the course of time.

An explanation for the findings of the current study might be that neuroticism represents a tendency to emotional lability with frequent negative affective states resulting in lower SWB. Accordingly, using an experience sampling method, Pos et al. have shown that negative affective states are associated with

poorer subjective well-being measured with the SWN-20 in daily life[36]. Furthermore, personality traits play a mediating role in the association between other contributors such as trauma in early childhood and negative affective states[35]. Extraversion on the other hand showed a positive mediating effect, serving as a protecting trait.

A second pathway explaining the association between personality traits and SWB might be related to different coping styles. The remaining correlation between higher neuroticism and subjective well-being after correction for state factors such as depressive symptoms, might be due to trait-like factors such as avoidant coping strategies and negative cognitive strategies, such as unrealistic fears and self-depreciation. Lysaker et al. have shown that neuroticism is associated with avoidant coping strategies in patients with schizophrenia[11,13]. Extraversion on the other hand is associated with problem oriented active coping styles and the ability to generate social support (reviewed by Phillips et al.[37]) and more positive affect states. Third, Vohs et al. have proposed intrinsic motivation as a common pathway between personality traits and psychopathology. They showed that intrinsic motivation is predicted by extraversion and is associated with negative symptoms[38].

Our findings are in line with the findings of other studies showing that personality traits are related to outcomes in schizophrenia such as symptomatology and quality of life and that these associations remain stable over time[39–41].

Several limitations need to be acknowledged. The sample size of participants completing all assessments (three to six years) was much smaller (n = 85) than the sample that only completed the first two assessments (n = 186, loss to follow up = 54.3%), resulting in reduced power. However, a subgroup analysis did not reveal significant differences in diagnosis, personality traits or the significant moderators of subjective well-being between those that dropped out and those that participated in all assessments. Moreover, the effects of the personality traits remained robust in the 3-6 year follow-up sample. This makes it less probable that a larger sample or better retention in the study would have changed the results substantially. Second, we were only able to collect SWN data for 3 measurements in six years. We do not know the variation of trajectories beyond these assessments. However, our findings are consistent with the findings of Lambert et al., who found a stable low, stable high and improving well-being groups[6,8].
Third, our sample consists of a relatively high educated, well-functioning patient group with comparable higher SWB, compared to the cohort investigated by Lambert and colleagues. This limits generalizability of the results. Fourth,

although antipsychotic medication use did not moderate the association between subjective well-being and personality traits, a differential effect of antipsychotic dosage on subjective well-being has been well established[42]. Future longitudinal cohort studies assessing subjective well-being should include thorough medication and adherence registration. Fifth, the emotional distress subscale of the PANSS does not fully encompass the symptoms of depressive disorders, e.g. suicidal thoughts and self-depreciation are missing. Therefore, we might have missed important components of the severity of depressive symptoms. In future studies this should be addressed by using for example the Calgary Depression Scale for Schizophrenia[43]. Finally, due to the observational design of the GROUP study, we cannot infer causality.

In conclusion, personality traits are associated with subjective well-being in patients with schizophrenia over the course of 6 years, over and above the influence of positive, negative and depressive symptoms. One in seven patients suffers from persistent low subjective well-being, which is related to higher levels of neuroticism and lower levels of extraversion. Neuroticism itself is associated with a higher risk for depressive and anxiety-related symptoms, increased stress-sensitivity and frequent negative affect states. The latter are associated with a decreased subjective well-being. Therefore, neuroticism (the tendency for negative affectivity) may be an important focus for therapeutic interventions in patients with schizophrenia. Preliminary evidence suggests that addressing more general domains such as behaviour activation, dysfunctional beliefs and coping strategies with cognitive behavioural therapy or acceptance and commitment therapy reduces negative affectivity and increases quality of life and functioning in patients with psychotic disorders[44,45].

Funding

The infrastructure for the GROUP study is funded through the Geestkracht programme of the Dutch Health Research Council (Zon-Mw, grant number 10-000-1001), and matching funds from participating pharmaceutical companies (Lundbeck, AstraZeneca, Eli Lilly, Janssen Cilag) and universities and mental health care organizations (Amsterdam: Academic Psychiatric Centre of the Academic Medical Center and the mental health institutions: GGZ Ingeest, Arkin, Dijk en Duin, GGZ Rivierduinen, Erasmus Medical Centre, GGZ Noord Holland Noord. Groningen: University Medical Center Groningen and the mental health institutions: Lentis, GGZ Friesland, GGZ Drenthe, Dimence, Mediant, GGNet Warnsveld, Yulius Dordrecht and Parnassia psycho-medical center The Hague. Maastricht: Maastricht University Medical Centre and the mental health institutions: GGZ Eindhoven en De Kempen, GGZ Breburg, GGZ Oost-Brabant, Vincent van Gogh voor Geestelijke Gezondheid, Mondriaan, Virenze riagg, Zuyderland GGZ, MET ggz, Universitair Centrum Sint-Jozef Kortenberg, CAPRI University of Antwerp, PC Ziekeren Sint-Truiden, PZ Sancta Maria Sint-Truiden, GGZ Overpelt, OPZ Rekem. Utrecht: University Medical Center Utrecht and the mental health institutions Altrecht, GGZ Centraal and Delta.)

Conflict of interest

Prof. dr. L. de Haan has received investigator initiated grants from Eli Lilly and Janssen-Cilag, more than 3 years ago.

Acknowledgments

We are grateful for the generosity of time and effort by the patients, their families and healthy subjects. We thank Matthijs Blankers for his invaluable help with the statistical analyses and we thank Floor Vergouwe her graphical help.

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CHAPTER 6

The affective and behavioural responses to life events, also referred to as coping styles, is associated with levels of subjective well-being. Negative life events and reduced subjective well-being are more prevalent in patients with psychotic disorders. The aims of the current study were to test a mediation model, with coping styles as potential mediators of the relation between negative life events and subjective well-being in patients with psychotic disorders (n = 259), and to repeat the potential mediation model in patients' non-affected siblings (n = 309). Data pertains to a sub-sample of GROUP, a Dutch naturalistic cohort study. The Subjective Well-being under Neuroleptics-20 (SWN-20) scale was used to assess subjective well-being. Coping styles were assessed with the Utrechtse Coping Lijst (UCL). Life events were assessed using an adaptation of the Interview of the Recent Life Event Scale (IRLES). Siblings, but not patients, who experienced negative life events in the previous three year period were more likely to experience a lower well-being. For both groups passive coping styles mediated the relation between negative life events and subjective well-being. Severity of positive, negative or affective symptoms did not change this relationship. Our findings point to a better recognition of coping styles as a therapeutic target to promote well-being and recovery.

COPING STYLES MEDIATE THE ASSOCIATION BETWEEN NEGATIVE LIFE EVENTS AND SUBJECTIVE WELL-BEING IN PATIENTS WITH NON-AFFECTIVE PSYCHOTIC DISORDERS AND THEIR SIBLINGS

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IN: PSYCHIATRY RESEARCH, 272 (2019), 296-303

Introduction

Patients with psychotic disorders experience poorer subjective well-being compared to their siblings[1] and to the general population[1–5]. Low subjective well-being can persist for several years[6,7] and is associated with lower chances of reaching symptom remission, restoring social functioning and reaching complete recovery[6]. Consequently, subjective well-being has become an important treatment outcome[8,9]. Clinical variables of influence on subjective well-being in patients with psychotic disorders are the severity of positive, depressive and negative symptoms and the dosage of antipsychotic medication[10]. In particular, subjective well-being is associated with dopamine D_2-receptor occupation by antipsychotic drugs. Subjective well-being was found to be associated with striatal dopamine D_2-receptor blockade is correlated to dosage of antipsychotic drugs (r = -0.66)[11]. However, symptom severity and medication do not fully explain the variance of subjective well-being in the long term[12]. The impact of individual characteristics, e.g. the personality traits and coping styles, on subjective well-being has been less extensively studied.

Assessment of subjective well-being overlaps with quality of life measurement, especially with the psychological sub-domain of the WHO-quality of life questionnaire[1]. Studies on quality of life in patients with a psychotic disorder show that subjective evaluations are related to various psychosocial concepts, for instance the personality trait neuroticism (negative affectivity)[13–15], the concept of self-efficacy[16] and the concept of coping styles[17–20].

Coping styles refer to cognitive and behavioural efforts to prevent, manage or alleviate stress[21]. The capacity to adapt to life events on a cognitive and affective level is associated with the level of subjective well-being in the general population[22]. Additionally, Diener[22] suggests that subjective well-being is related to having an internal locus of control[23], meaning being able to attribute outcome to oneself instead of to external causes[24]. Furthermore, significant interactions between locus of control and coping strategies have been reported. Parkes et al.[25] showed that individuals with internal attribution reported more adaptive coping strategies than those with external locus of control. In clinical research, coping is often conceptualized as a mediator between a stressor and clinical, functional or evaluative outcome. Patients with psychotic disorders face the challenge of coping with different types of stressors, including symptoms[26–29] as well as everyday life events[30–32]. In patients with psychotic disorders, coping

styles have shown to act as mediators for quality of life measures; Ritsner et al.[19] found that emotion-oriented coping styles partially mediate the relationship between the distress of psychopathology (anxiety/depression, severity of activation) and psychological distress on the one hand and subjective quality of life, on the other hand. López-Navarro found that problem focused coping styles mediate the relation between positive symptoms and the WHOQOL-psychological subdomain[33].

Among the limited amount of studies in this field, Ritsner et al.[19] showed that task oriented strategies and distraction from the stressor, here assessed with social diversion or a substitute task, is positively correlated with levels of quality of life in patients with psychotic disorders. In line with this finding, Caron et al.[17] found that the coping strategy 'putting effort in changing the situation' is positively correlated with quality of life. Holubova et al.[34] found positive associations between quality of life and reaction control, positive self-instruction, underestimation, diversion and compensatory satisfaction. Additionally, two studies found that resilience coping (e.g. controlling one's reaction[35] or regulating the emotional response[36] buffered the effects of traumatic experiences on psychiatric symptoms, levels of distress and social support[35,36]. Identified coping styles that correlate negatively with quality of life are emotional oriented strategies (emotional responses, self- preoccupation, and fantasizing reactions)[19] and escape tendency, perseveration, resignation, and self-accusation[34]. Aforementioned studies have addressed coping styles within different conceptual frameworks. Taken together, active and problem focused strategies seem to positively influence well-being. Emotion oriented and passive strategies seem to negatively affect well-being. Of note, Lazarus and colleagues suggest that passive coping styles are among the emotion-focused styles and are thought to have a transient effect on stress[(22, in 40)]. However, by contrast, Rudnick et al.[26] found no association between emotion-oriented or problem–oriented coping styles and quality of life, which could be related to insufficient power due to a relatively small sample size (n = 58).

So far, the potential mediating effect of coping styles on the association between recent life events and subjective well-being in patients with a psychotic disorder has not been studied. In the current study, we will focus on a cohort of patients with psychotic disorders and their healthy siblings to investigate whether similar associations exist across subjects with different degrees of vulnerability for psychosis. Including first-degree relatives serves as a replication in subjects with a liability for psychosis, but without illness related possible confounding effects of impairment or medication.

In the current study, (I) we aim to investigate the relation between coping styles and subjective well-being in both patients with a non-affective psychotic disorders and their healthy siblings, hypothesizing that active and problem focused coping strategies are positively correlated to subjective well-being and that passive and avoidant strategies are negatively associated in both groups. We expect in siblings a higher occurrence of active and problem focused coping styles. (II) We aim to investigate the relation between recent negative life events and subjective well-being in patients and healthy siblings, hypothesizing that a negative association between negative life events and subjective well-being exists both on a clinical and sub-clinical level in patients and siblings. Finally, (III) we will explore whether coping styles mediate the relation between negative life events and subjective well-being in both patients and siblings.

Methods

2.1 Procedure and sample

Data pertain to a sub-sample (third assessment, data release 5.0, Amsterdam, Utrecht and Groningen regions) from the Genetic Risk and Outcome of Psychosis (GROUP)-study cohort; a multi-center, longitudinal naturalistic cohort, designed to facilitate studying vulnerability and resilience factors for variation in the expression of non-affective psychosis disorders. Patients were included at baseline, from in- and outward patient case-loads of the participating academic and regional mental health care centres. First degree brothers and sisters were recruited via their diagnosed relative. We included subjects with available data on subjective well-being, coping and recent life events: 259 patients and 309 siblings completed all questionnaires.

Inclusion criteria for patients and siblings were:

1. age range of 16 to 50 years and;
2. good command of the Dutch language.

Patients had to meet DSM-IV-TR criteria for a non-affective psychotic disorder[38] which was assessed with the Comprehensive Assessment of Symptoms and History (CASH[39] or the Schedules for Clinical Assessment for Neuropsychiatry version 2.1 (SCAN[40]). An additional inclusion criterion for the sibling group was the absence of a lifetime psychotic disorder. A further detailed description of the study design, sampling and inclusion criteria can be found elsewhere[41].

The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht (04/003-O) and subsequently by local review boards of each participating institute.

2.2 Instruments

We used the Subjective Well-being under Neuroleptics scale[42]; short form (SWN-20) to measure subjective well-being. The SWN is the most widely used instrument to measure subjective well-being[1,43]. Participants mark 20 statements on emotional regulation, social integration, physical functioning and mental functioning during the last week on a six-point Likert scale. The five domains load on a single factor structure[1]. The original extended version of the SWN has a high internal consistency: Cronbach's alpha of 0.95 for overall score and 0.63 to 0.82 for each of the five subdomains[42]. The SWN-20 shows a correlation of 0.98 with the original SWN.

Coping styles were assessed with the Utrechtse Coping Lijst (Utrecht Coping List, UCL)[44]. The UCL is a self-rating questionnaire measuring 7 coping strategies[45]. The 7 subscales include proactive acting, passive reacting, avoiding, palliative reacting, seeking social support, expression of emotions and calming thoughts. It has good psychometric properties including moderate to good internal consistency (Cronbach's alpha coefficients ranging from 0.64 to 0.82) and reasonable test–retest reliability (0.52 to 0.79), assessed in the healthy population[44].

Negative life events over the past 3 years were assessed with a Dutch translation of a list of events based on the Interview of the Recent Life Event Scale (IRLES[46]), which was first described by Jacobs and colleagues[47]. Subjects report whether or not they have experienced positive or negative life events and rate the impact of experienced events on a 5-point Likert scale varying from 1 (very unpleasant) to 5 (very pleasant). The list contains 61 life events, divided into 10 categories: work, education, finance, physical health, bereavement, migration, courtship and cohabitation, legal, family and social relationships, and marital relationships, all representing datable occurrences involving changes in the external social environment[47]. Events with an unpleasant subjective appraisal (score 1 or 2) were counted to a score representing the amount of negative life events and a continuous exposure variable was calculated representing the number of such unpleasant events[48,49].

The Positive and Negative Syndrome Scale (PANSS) was used to evaluate symptom domains at all assessments[50]. The PANSS is identified to have a good

validity and reliability[51]. We used the positive and negative symptoms from the 5-factor model (positive symptoms, negative symptoms, disorganization, excitement and emotional distress) as developed by Van der Gaag et al.[52]. This is a commonly used model with a good face validity and a satisfactory goodness-of-fit (Comparative Fit Index = 0.905; Root Mean Square Error of Approximation = 0.052). It consists of five factors. We used the PANSS emotional distress subscale as a measure of severity of affective symptoms.

For the siblings, we used the Community Assessment of Psychic Experiences (CAPE;www.cape42.homestead.com) to administer self-reports psychotic experiences in the past three years. The questionnaire consists of 42 items in total, 20 questions on positive symptoms (e.g. 'Do you ever feel as if things in magazines or on TV were written especially for you?'), 14 on negative symptoms (e.g. 'Do you ever feel that you are lacking in motivation to do things?') and 8 on depressive symptoms (e.g. 'Do you ever feel sad'). The symptoms are measured using a 4-point Likert scale, assessing the frequency varying from 0 (never) to 3 (nearly always). With a validated three-factor structure of positive, negative and depressive dimensions, the CAPE is a reliable measure to register sub-clinical psychotic dimensions in the healthy population[53,54].

2.3 Data analysis

Differences in baseline characteristics between the patients and siblings were assessed with t-tests and χ^2-tests. We compared the gender distribution, IQ-estimates, the baseline subjective well-being, the occurrence of coping styles and the amount of experienced life events between patients and siblings. Antipsychotic medication (y/n) use was an additional covariate for patients.

Pearson's correlation was used for zero order associations between the negative life events, coping and subjective well-being. Spearman's rho was used for non-normally distributed outcomes.

We tested a mediation model, by directly testing significance of the indirect effect (ab) of negative life events on subjective well-being through the coping styles as parallel multiple mediators in a regression model[55,56]. The negative life events-coping style path is noted a, the coping-subjective well-being path is noted b. Following the suggestions of Hayes and colleagues the mediators with a significant zero order correlation to subjective well-being in either the patient or the sibling sample were entered simultaneously so that we could assess the indirect effects of all coping styles while controlling for the negative life events.

For the indirect effects, a bootstrapping approach was used, taking the mean of 5000 estimates of ab and the 95% confidence interval. The presented path coefficients are unstandardised. Significance levels of 0.05 were accepted.

Finally, to account for the possible confounding effect of symptom severity and gender, covariates were added to the model. All analyses were performed with SPSS version 24.

Results

See Table 1 for socio-demographic characteristics and the comparison between patients and siblings. The sibling sample contains significantly more females and siblings had a higher mean IQ. Patients reported a lower mean subjective well-being than siblings. The incidence of life events was not significantly different.

Coping styles occurred differently across the two samples. Patients reported a significantly higher incidence of palliative reaction, avoidance/await, passive reaction and using calming thoughts. Siblings more often employed proactive action and the expression of emotions. Seeking social support was applied equally often in both groups.

3.2 Association between coping styles and subjective well-being

Scores for subjective well-being and coping styles were normally distributed among both samples. In patients, the coping styles proactive acting, seeking social support and using calming thoughts were positively associated with subjective well-being. Passive reacting, avoiding and palliative reacting were negatively associated with subjective well-being. Expression of emotion was not significantly related to the SWN total score. For more detailed information, see Table 2.

Siblings showed a positive association between subjective well-being and the coping styles proactive acting and seeking social support. Expression of emotions, passive reacting, avoiding and palliative reacting were significantly negatively associated with the subjective well-being. Using calming thoughts was not significantly related to subjective well-being in siblings.

Table 1: sample characteristics.

	patients (n = 259)	siblings (n = 309)	MD	χ^2/ *t*-test	*p*-value
age (M, SD)	34 (8.0)	35 (8.0)			
gender (n, %)					
male	191 (73.7)	138 (44.6)	-	48.9	< 0.001
female	68 (26.3)	171 (55.4)			
ethnicity (n)					
causasian	209 (80.7)	270 (87.4)			
moroccan	8 (3.1)	5 (1.6)			
surinamese	10 (3.9)	5 (1.6)			
turkish	2 (0.1)	2 (0.06)			
asian	1 (0.0)	1 (0.0)			
other	7 (2.7)	1 (0.0)			
mixed	16 (6.2)	23 (7.4)			
unknown	6 (2.3)	2 (0.1)			
diagnosis (n, %)					
schizophrenia	203 (78.4)				
schizoaffective disorder	27 (10.4)				
other psychotic disorder	29 (11.2)				
duration of illness (years, M, SD)	10.8 (47)				
WAIS estimated total IQ (M, SD)	103 (19)	113 (18)	10.5	*t* = 5.98	< 0.001
current use of antipsychotics					
currently using	167 (64.5)	-			
not currently using	14 (5.4)	-			
unknown	78 (30.1)	-			
PANSS					
positive symptoms	11 (6)				
negative symptoms	12 (5)				
emotional distress	13 (5)				
CAPE (freq.)					
positive symptoms		0.08 (0.1)			
negative symptoms		0.48 (0.4)			
emotional distress		0.52 (0.4)			
SWN-20 (M, SD)	88.91 (13.9)	98.77 (11.6)		*t* = 9.22	< 0.001
UCL					
proactive action	2.50 (0.50)	2.74 (0.47)	0.25	*t* = 6.02	< 0.001
palliative reaction	2.27 (0.45)	2.13 (0.43)	-0.14	*t* = -3.92	< 0.001
avoidance/wait	2.20 (0.41)	1.99 (0.38)	-0.21	*t* = -6.40	< 0.001
seeking social support	2.29 (0.53)	2.36 (0.57)	-0.07	*t* = 1.46	0.145
passive reaction	1.98 (0.57)	1.58 (0.49)	-0.14	*t* = -9.15	< 0.001
expression of emotion	1.93 (0.51)	2.08 (0.51)	-0.21	*t* = 3.35	< 0.001
calming thoughts	2.40 (0.54)	2.37 (0.47)	-0.03	*t* = -0.73	0.463
negative life events					
amount	3.02 (2.77)	3.22 (3.15)	-0.20	*t* = -0.80	0.43

Table 2: First-order correlations (r) of the coping styles and subjective well-being.

Pearson's correlation		SWN-20	
		patients (n = 259)	siblings (n = 309)
UCL			
	proactive action	0.47***	0.36***
	palliative reaction	-0.083	-0.19**
	avoidance/await	-0.30***	-0.38***
	seeking social support	0.20**	0.25***
	passive reaction	-0.64***	-0.65***
	expression of emotion	-0.002	-0.14**
	calming thoughts	0.22**	0.083

** $p < 0.01$; *** $p < 0.001$

3.3 Association between the severity of negative life events and subjective well-being

Life events were not normally distributed. In patients, the amount of negative life events was not correlated with subjective well-being (Spearman's rho .-0.065, two-tailed $p = 0.299$).

In siblings, negative life events were negatively associated with subjective well-being (Spearman's rho -0.12, two tailed $p = 0.04$).

3.4 Mediating effects of coping styles between negative life events and subjective well-being

Figure 1 shows the mediation model with the coping styles entered simultaneously. Table 3 shows the direct and indirect effects of negative life events on subjective well-being in patients and siblings, referred to as c'. The indirect effects are presented as the product of the association between negative life events and the coping styles (a) and the effect of coping styles on subjective well-being (b). Bootstrapped confidence intervals (95% CI) are displayed for both the direct and the indirect effects. When both upper and lower estimates of the 95% CI are smaller or larger than 0, significance of the effect is indicated.

Mediation occurred through passive reacting in both patients and siblings. In addition, in patients, proactive action taking mediated the association between life events and SWN on a trend level (indirect effect = 1.3, CI 0.25 – 2.7). The overall model fit for patients was R^2 0.57, $p < 0.001$ and for siblings: R^2 0.53, $p < 0.001$). Correction for potential confounding effects of gender, antipsychotic drug use and symptom severity, showed that only positive, negative and depressive symptoms contributed significantly to the model, but that all indirect effects remained significant (unstandardised coefficients respectively, positive: 0.35, p

= 0.019, negative: -0.32, p = 0.011, depressive symptoms: -0.61, p = 0.001). In the sibling sample, sub-clinical negative and depressive symptoms significantly contributed to the model (unstandardised coefficients respectively, negative -5.03, p = 0.009, depressive symptoms = -3.85, p = 0.048) but the indirect effect of passive reacting remained significant.

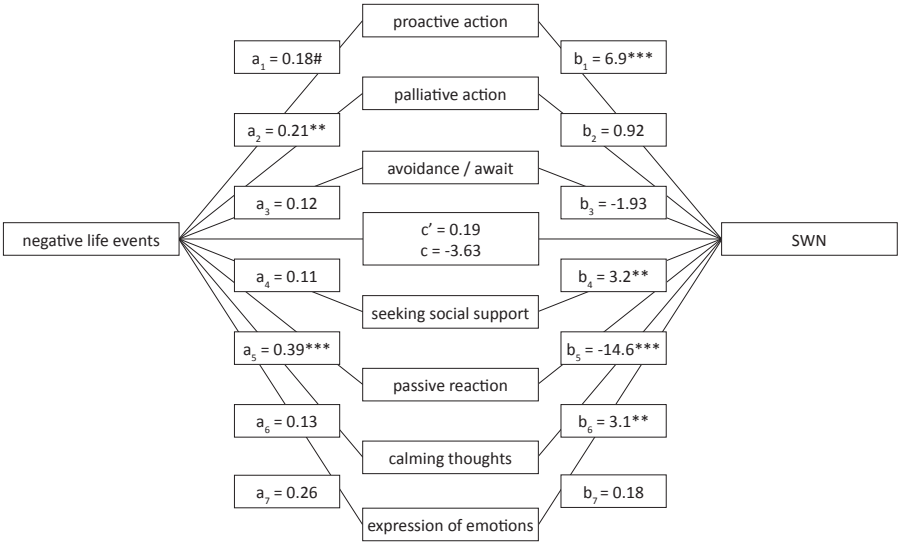

Figure 1. Mediation model for patients depicting the direct and total effects of negative life events on subjective well-being.

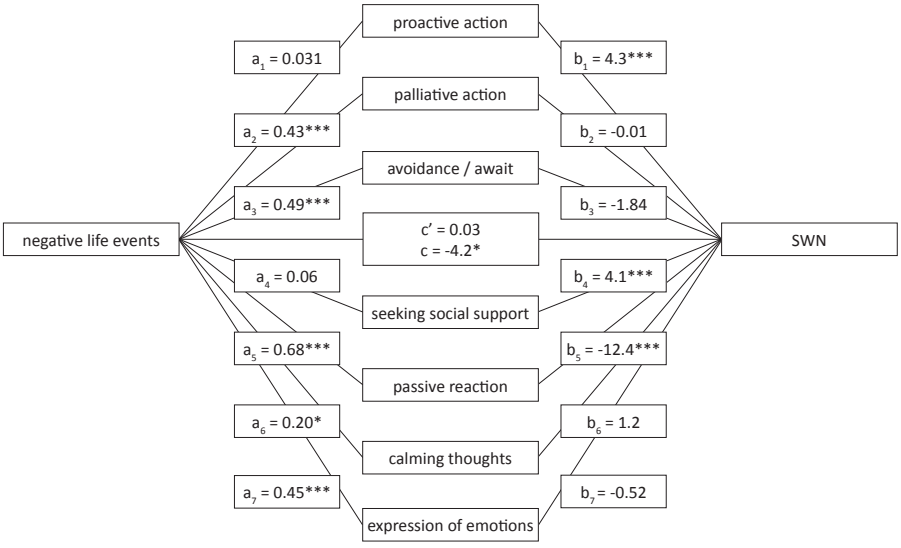

Figure 2. Mediation model for siblings depicting the direct and total effects of negative life events on subjective well-being.

Table 3: Summary of mediation analysis in patients (n = 259) and siblings (n = 309)

			indirect effect	total effect
X	M	Y	ab (95% CI)	c
patients	UCL			
negative life events	proactive action	SWN-20	1.3 (0.25 — 2.7)†	-3.55
	palliative reaction		0.19 (-0.29 — 0.95)	
	avoidance/await		-0.27 (-1.03 — 0.06)	
	seeking social support		0.39 (-0.73 — 1.14)	
	passive reaction		-5.6 (-7.9 — -3.4)†	
	expression of emotion		0.05 (-0.37 — 0.62)	
	calming thoughts		0.48 (-0.02 — 1.4)	
siblings				
negative life events	proactive action	SWN-20	-0.13 (-0.97 — 0.54)	-9.2*
	palliative reaction		-0.43 (-1.7 — 0.50)	
	avoidance/await		-0.49 (-1.4 — 0.14)	
	seeking social support		0.23 (-0.46 — 1.14)	
	passive reaction		-8.42 (-11.3 — -6.2)†	
	expression of emotion		-0.23 (-1.11 — 0.49)	
	calming thoughts		0.24 (-0.07 — 0.88)	

Discussion

The current study investigated the relation between negative life events, coping styles and subjective well-being in patients with a non-affective psychotic disorder. Healthy siblings were studied to explore whether associations are also present on a sub-clinical level in subjects who share the vulnerability for a psychotic disorder but do not experience illness related confounding effects. When comparing the two groups, siblings employed a higher rate of proactive coping, whereas patients more often reported passive reacting, palliative reacting and avoidant strategies. Both patients and siblings who employ proactive action taking and seeking social support generally report a higher subjective well-being. Additionally, passive coping was associated with a lower subjective well-being in both patients and siblings. These findings confirm our first hypotheses: proactive coping styles and seeking social support are positively related to subjective well-being across subjects with a dimensional liability for psychotic disorders and are more often applied by healthy siblings.

Furthermore, we found that the patients who use palliative and passive coping reactions were more likely to report having experienced negative life events in the past three years. In siblings, additionally the use of calming thoughts and avoidant strategies were associated with more negative life events. In siblings, but not in patients, experiencing negative life events in the past three years was negatively associated with current subjective well-being. The absence of a statis-

tically significant direct relationship between negative life events and subjective well-being in the patient sample was unexpected. Patients did not experience fewer negative life events than siblings in the past 3 years.

In both groups we found that passive coping mediated the association between negative life events and subjective well-being. In patients, we found proactive action taking as a positive mediator between life events and subjective well-being. Gender and comorbid (sub)clinical positive, negative or depressive symptoms did not substantially change theses associations. Our findings regarding the relationships between coping styles and subjective well-being are generally in line with the findings of studies that investigated coping in relation to similar concepts of subjective experiences[19,34,57].

Regarding possible underlying mechanisms, the mediating effects of passive coping fit within the locus of control theory[23], hypothesizing that the less one experiences an internal locus of control, the more dysfunctional coping styles are used. Dysfunctional coping patterns have shown to be related to fatalistic external biases in patients with a first episode of psychosis[58]. Also, having an internal locus of control is associated with better recovery rates in patients with schizophrenia[59]. However, since no studies so far have evaluated the locus of control theory in relation to subjective experiences in patients with a psychotic disorder, this needs further exploration in future research. Studies have shown that patients with schizophrenia more often report a less internal and a more external locus of control[59,60].

Similar results in both patients and siblings regarding passive reaction suggests that these dysfunctional coping strategies are not solely related to the experience of a distinct psychotic disorder, for example as a consequence of negative symptoms. Instead these coping strategies might rather be related to negative affectivity in stressful situations connected to reacting with inactivity and rumination (demonstrated by items such as 'letting things go' and 'ruminating about the past'). Of note, the mediational role of proactive coping styles on subjective well-being in patients has been found earlier by López-Navarro et al.[33]. Yet, the cross-sectional, observational nature of our study precludes causal interpretations.

Some limitations of the current study should be mentioned. First, due to the cross-sectional design causality cannot be inferred. It has been suggested that coping styles develop over time[18], for example as an automated response to a prolonged period of mood disturbance[61]. Hence, reciprocal causation is possi-

ble. Second, we did not find a significant c'-path (direct effect of negative life events on SWB) in the mediation analysis in the patient sample. Nevertheless, according to Hayes and colleagues, the method we used is able to provide an approach for understanding a mechanism. They advocate for directly testing the significance of the indirect effects using a regression model and a bootstrapping approach. However, a replication study would be of importance. Third, we used the emotional distress subscale of PANSS for affective symptoms in patients, which is an unspecific scale to assess severity of depressive symptoms. Therefore, we might have missed components of the severity of depressive symptoms. The Calgary Depression Scale for Schizophrenia would have been a better alternative, but was unfortunately not administered at the third assessment in GROUP. We were not able to use the CAPE depression subscale for this purpose since the CAPE depression subscale was not complete for the patient sample. Fourth, gender distribution is different across the samples, yet we did not find a confounding effect of gender on the mediation model. Fifth, our finding that the use of antipsychotic medication did not moderate the relationships between life events, the coping styles and subjective well-being in the mediation model, should be interpreted with the possibility in mind that more detailed information on dose and compliance alter this conclusion. Since the differential effects of antipsychotic medication use on subjective well-being are well established 10, future research should include registration of dose and compliance. When assessing passive coping styles in clinical practice, clinicians will have to consider whether a dampened salience or sedating effects associated with antipsychotic medication could be a cause. Sixth, we used a specific structure of coping styles while the debate concerning the best way to arrange coping styles in an adequate hierarchic or functional structure is still ongoing[62,63]. The items of the UCL do not follow the hierarchy of coping styles as proposed by Connor-Smith and colleagues[65]. Due to missing information on antipsychotic use, the use of self-reported instruments in assessing coping strategies and restricted availability of specific measures of depressive symptoms, we cannot rule out the effect of unmeasured factors.

In conclusion, passive coping to negative life events is associated with worse subjective well-being in both patients with psychotic disorders and their non-affected siblings. Our study underlines the importance of individual characteristics in subjective well-being of patients with a psychotic disorder. Further studies are needed to evaluate whether improving active coping strategies may enhance subjective well-being in patients suffering from schizophrenia or related disorders.

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CHAPTER 7

Acknowledging the patient's perspective and aiming for an optimal subjective well-being is crucial for a good therapeutic relationship and enhances treatment adherence. This thesis aimed to describe the development of a shared decision making tool that supports patients in their choice for a specific antipsychotic agent. The second aim of this thesis was to increase the understanding of pharmacological and psychological factors related to subjective well-being, in order to identify possible targets for intervention.

SUMMARY AND GENERAL DISCUSSION

Main findings in consecutive chapters in their context

Chapter 2. The Personal Antipsychotic Choice Index

This chapter presents the development of the Personal Antipsychotic Choice index. As shared decision making is thought to improve adherence, we developed an online decision aid for the choice of antipsychotic medication. A review of the literature showed that high-level evidence was available for ranking weight gain, sexual dysfunction, menstrual disorders, extrapyramidal symptoms and effectiveness on psychotic symptoms.

Patients can rank the importance of three distinct effects of antipsychotics (effect on positive, depressive and cognitive symptoms) as well as the perceived acceptability of 14 often occurring adverse effects. The combination of evidence and patients' preferences according to their response on each item results in a personalized ranking of antipsychotics which patients can discuss with their clinician.

By describing our procedure transparently, we provide a tool that is easy to update with future findings from clinical trials. A current limitation of the PACindex is the lack of high level evidence regarding depressive and cognitive symptoms, drowsiness, hypersomnia, anticholinergic adverse effects, hypersalivation, nausea, dizziness, energy loss, blunted affect/less need for companionship. Moreover, the available evidence is based on group averages and since individual effects can diverse substantially, the ranking order given by this tool should always be interpreted as an indication. Patients are warned that the advice offers an indication and should be discussed with a clinician.

The PACindex is the first electronic shared decision making tool developed for patients to assist in choosing antipsychotic medication. Future research into the effectiveness of the PACindex should focus on whether consultations with the PACindex are more client centred than consultation-as-usual, whether patients feel more empowered and whether the work alliance benefits. Another question of interest is whether patients who used the PACindex, are more satisfied with reached decisions and subjectively report less impairing side effects. Answering those questions in the future could be of value in preventing relapse. In a meta-analysis, Haddad et al. have shown that psycho-education, shared decision-making and promoting a positive therapeutic alliance are indeed key factors for promoting adherence[1]. Meanwhile, the literature review and the de-

velopment of the PACindex provide a point of reference for further research into the effectiveness of an electronic decision aid on the quality and impact of shared decision making.

Chapter 3. Dopamine D_2-receptor affinity of antipsychotics in relation to subjective well-being in patients with a psychotic disorder

Subjective well-being under neuroleptic treatment is influenced by the degree of blockage of the dopamine D_2-receptor by the antipsychotic agent. It is still open to debate whether the receptor affinity of an antipsychotic further influences subjective well-being at similar receptor occupancies.

In this chapter, we investigated whether high levels of estimated D_2-receptor affinity are associated with a lower subjective well-being in a sample of the GROUP-study, a naturalistic cohort of patients with psychotic disorders. We found no differences between three groups of tight, intermediate and loose binding antipsychotics, after correction for the dosage. Switching to a different binding group was neither associated with change in subjective well-being. Hence, we found no support for the hypothesis that high dopamine D_2-receptor affinity of antipsychotic medication is associated with poorer subjective well-being.

These findings are in line with three studies that did not show differences in subjective well-being between antipsychotic agents with the same level of D_2-receptor occupancy[2–4]. However, the negative findings of our study might imply that the effects of differences in D_2-receptor binding between antipsychotic agents on subjective well-being are not large enough to be detected in a study with a naturalistic design. A study with a better registration of medication compliance, ideally accompanied by neuroimaging techniques, would provide a more solid framework to refute the hypothesis. A double blind RCT would be able to measure the effect of antipsychotics of different D_2-receptor affinities, yet an alternative would be a larger observational cohort of with a longer follow-up that allows for within subject comparisons.

One other question at hand is whether factors that we did not include, might be of larger influence on subjective well-being than receptor affinity. Personality, self-esteem, cognitive functioning and differences in metabolism and neurotransmission have shown to be also related to subjective well-being[5].

For clinical practice, our study suggests that optimal dosing of an antipsychotic agent is more important for subjective well-being than the choice of the agent based on its D_2-receptor affinity.

Chapter 4. An experience sampling study on the ecological validity of the SWN-20: Indication that subjective well-being is associated with momentary affective states above and beyond psychosis susceptibility

We investigated the ecological validity of the SWN-20, the most commonly used tool to assess subjective well-being in patients with psychotic disorders. The SWN-20 was compared to results measured with the experience sampling method (ESM). Again with data of the GROUP-cohort, we analysed the associations between SWN-20 scores and momentary positive affect, negative affect, reward experience and stress-sensitivity. We found that higher subjective well-being was associated with higher momentary positive affect (means score on items: cheerful, satisfied, relaxed, enthusiastic) and lower negative affect (insecure, down, lonely, anxious, irritated), confirming our hypothesis. Also, these associations were the same for patients and siblings, showing that the findings are generalizable to the healthy population. This in line with Vothknecht et al.[6] who found evidence for validity of the SWN-20 to assess subjective well-being across groups that have a different vulnerability to develop psychosis (patients, siblings and healthy subjects).

On the one hand, the ESM method provides important insight into everyday moment to moment affective states in patients. For example, Oorschot et al.[7] demonstrated that patients with schizophrenia experienced equal levels of positive affect in response to pleasant activities ('reward experience') compared to healthy controls, but interestingly, patients experienced fewer pleasant activities, explaining the lower overall levels of positive affect. ESM is however time consuming and therefore demanding, On the other hand, the substantial association between SWN scores and ESM data propose that the SWN-20 is a more easy-to-use and ecologically valid tool to measure subjective well-being in people with different vulnerability for psychosis.

Chapter 5. A longitudinal analysis of the effects of neuroticism and extraversion on subjective well-being in patients with schizophrenia
and
Chapter 6. Coping styles mediate the association between negative life events and subjective well-being in patients with non-affective psychotic disorders and their siblings

The subjective well-being of patients with a psychotic disorder is only partially influenced by symptom severity and the use of antipsychotic medication[5,8]. Chapter 4 and 5 describe the associations of personality traits and coping styles with subjective well-being, using data from the GROUP-cohort. We assessed whether neuroticism and extraversion as measured with the Five Factor Inventory are related to subjective well-being in both patients and healthy controls. We found that 1 in 7 patients suffered from a persistent low subjective well-being, which is related to higher levels of neuroticism and lower levels of extraversion, regardless of severity of positive, negative or depressive symptoms. Our findings are in line with earlier literature on the cross-sectional association of quality of life and personality traits in patients with a psychotic disorder[9–11]. Our results show that this association remains stable over the course of time.

In sum, neuroticism seems to be an indicator for risk of long term low subjective well-being. Neuroticism can be expressed as the tendency to experience negative affect and a strong variability in negative affect in reaction to stressors[12]. One of the pathways between how personality traits and subjective well-being are related, might be via how a person copes with stressors. Coping styles are the affective and behavioural manners of how we relieve stress (e.g. caused by life events) and negative affectivity.

We tested a mediation model, with coping styles as potential mediators of the relation between negative life events and subjective well-being in patients with psychotic disorders. We also found evidence for the mediation model in patients' non-affected siblings. Siblings, but not patients, who experienced negative life events in the previous three year period were more likely to experience a lower well-being. For both groups passive coping styles mediated the relation between negative life events and subjective well-being, even after accounting for the severity of positive, negative or affective symptoms. In patients, we found also proactive action taking as a positive mediator between life events and subjective well-being. Our findings regarding the relationships between coping styles and subjective well-being are generally in line with the findings of studies that investigated coping in relation to similar concepts of subjective experiences[13–15].

The correlational modelling provides no causal understanding of the associations. For example, it has been suggested that coping styles develop over time[16], e.g. as an automated response to a prolonged period of mood disturbance[17]. To infer causal processes, future studies with prospective designs and more frequent assessments are needed.

For clinical practice, integrating the identification and improvement of coping styles in the long-term treatment plan for patient, might have a positive impact on the subjective well-being of patients with a psychotic disorder. Preliminary evidence shows that addressing more general domains such as behaviour activation, dysfunctional beliefs and coping styles with cognitive behavioural therapy, acceptance and commitment therapy or newer third wave psychotherapies, reduces negative affectivity and increases quality of life in these patients[18–20]. We have shown the importance of personality characteristics for subjective well-being of patients with a psychotic disorder and suggest these as a target for therapeutic interventions.

Strengths and limitations of this thesis

For chapters 3 to 6, data from the GROUP-cohort were used, which consists of patients with psychotic disorders, healthy siblings and controls. Therefore investigating this cohort allows for evaluation subjective well-being in psychotic disorders that include a naturalistic comparison to healthy individuals and siblings, who share genetic and environmental factors with patients, but do not suffer from disorder-related confounding factors such as social stigma, medication use and psychosocial deterioration as result of psychopathology, such as poor housing and poverty. The GROUP-cohort also contains the longest follow-up of subjective well-being to date and hence enabled us to study longitudinal patterns of subjective well-being in relation to psychological trait and state factors.

Some general limitations need to be mentioned as well. Although longitudinal observational cohort studies strongly aid in studying tentative causal relationships, the results do not allow for definitive statements on causality. Furthermore, it might be difficult to generalize our results to other samples due to the demanding nature of participation in the GROUP-study and subsequent selection bias. Although this contributes to homogeneity of the sample, we might have missed a lower functioning group of patients that is not capable of consenting to multiple days of testing. Furthermore, some instruments were only completed at only one or two research sites (such as the Five Factor Inventory), which has resulted in different sub samples of the GROUP-cohort per chapter.

From previous studies performed on the GROUP-cohort, it has become clear that it is a relatively high-functioning group of patients. It would be of value to include patients with more severe psychopathology and psychosocial problems, so that the relative contribution of personality characteristics and coping styles can be more adequately demonstrated in a sample better representing the treated prevalence of patients with a schizophrenia spectrum disorder.

Clinical and research implications of this thesis

The overarching theme of this thesis is the importance of the subjective experience of a patient with a psychotic disorder in the treatment process. The traditional role of the psychiatrist who diagnoses psychosis and prescribes medication to the psychotic person is old-fashioned and insufficient. Only patients can describe their experience during psychosis treatment in a valid way and acknowledging their perspective enhances collaboration and compliance to therapy. When treating psychosis, not only clinical recovery but also personal recovery should be targeted[21]. Studying subjective outcome measures is necessary for the emancipation of patients with (severe) mental illness. Currently, this is beginning to put in to practice by the field of positive psychiatry. Theoretical models are being introduced to study the process of recovery of patients with psychotic disorders, and that do not only focus on symptom remission but integrate the subjective well-being as an independent outcome (some even plead for well-being as the only outcome measure). Additional focus is placed upon improving hope, autonomy and self-efficacy of a person with a mental illness.

In chapter 4, 5 and 6, we approach subjective well-being from different angles that all relate to stress-sensitivity and -management. Our findings that neuroticism (reacting with negative affectivity to stress) and a passive reaction to stressful life events are associated with lower levels of subjective well-being, can be seen in light of to what extent a person experiences themselves as an active agent[22]: experiencing an internal locus of control presumably renders patients more content then when they experience the source of control outside of themselves. Subjective well-being in patients with a psychotic disorder has been associated with a feeling of competence and control over their own recovery process[23]. Likewise, people who experience control over their daily life, experience less difficulties in taking decisions in their treatment plan during shared decision making[24].

Naturally, the subjective experience of a person is best assessed and valued in a personal narrative and within a lasting therapeutic relationship. The operation-

alization of subjective well-being into questionnaires such as the SWN-20 was necessary to evaluate aspects that influence the subjective experience. However, in the research field of subjective well-being for severe mental illness there are currently 19 different instruments that assess well-being or the subjective quality of life[25]. Given the sensitivity for medication changes of the SWN-20 and, according to studies in this thesis, the tentative association to psychological correlates of subjective well-being, we plead for the continued use of the SWN-20 as an independent outcome measure in both pharmacological trials as well as in research focusing on resilience and personal recovery.

Conclusion

This thesis describes studies on the subjective well-being of patients with a psychotic disorder. The subjective evaluation of a patient's physical and mental state, defines how he or she evaluates medication use and the quality of the received care and to what extent he or she cherishes hope to be able lead a meaningful life.

With the PACindex, the first shared decision making tool for supporting patients in prioritizing and choosing a specific antipsychotic agent, we hope to provide a point of reference for further research into the effectiveness of an electronic decision aid, and into its effects on shared decision. Furthermore, we suggest that optimal dosing of an antipsychotic agent is more important for subjective well-being than the choice of the agent based on it's D_2-receptor affinity. Third, we found support for the ecological validity of the SWN-20 to measure day-to-day momentary affective states. Finally, we found that 1 in 7 patients keeps having a low subjective well-being over the course of six years. We demonstrated that the personality trait neuroticism contributes to such a trajectory, regardless of psychotic symptoms or the use of antipsychotic medication. Next, we tentatively found that active coping styles contribute to a better subjective well-being of patients with a psychotic disorder. On the contrary, passive reacting to negative life events seems to reduce subjective well-being. We suggest neuroticism and coping styles as a target for therapeutic interventions to improve resilience.

With this thesis, I hope to contribute to the body of knowledge on the subjective experience of people with a psychotic disorder, so that this knowledge can be used to improve the well-being of patients with schizophrenia and related disorders.

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APPENDIX

Nederlandse samenvatting

Introductie

Dit proefschrift gaat over het perspectief van de patiënt die aan schizofrenie lijdt.

Het perspectief van de patiënt en gedeelde besluitvorming

Meer dan de helft van de patiënten met een eerste psychose (zie box 1.) heeft na 4 jaar de medicatie (zie box 2.) gestaakt[1]. De belangrijkste, in principe veranderbare, factor om medicatietrouw te vergroten, is de kwaliteit van de therapeutische relatie tussen patiënt en behandelaar[2]. Patiënten met schizofrenie waarderen het als ze worden betrokken in de keuzes over starten, stoppen en bepalen van een middel. Een psychotische stoornis hebben staat het prioriteren van informatie en voorkeuren aangeven niet in de weg[3,4]. Om patiënten actief bij hun behandeling te betrekken is het nodig dat ze goed geinformeerd worden en dat de wetenschappelijke kennis betreffende medicatie wordt afgewogen op grond van hun persoonlijke voorkeuren.

De subjectieve evaluatie van een patiënt over diens' mentale en fysieke toestand tijdens een psychosebehandeling bepaalt voor een groot deel of iemand hoop ervaart dat de geboden behandeling zinvol kan zijn. Die subjectieve evaluatie laat zich uitdrukken in de term 'subjectief welbevinden'. Subjectief welbevinden kan worden gemeten. De meest gebruikte en onderzochte vragenlijst hiervoor is de Subjective Well-being under Neuroleptics scale (SWN-20). Patiënten die een goede subjectieve ervaring tijdens behandeling met antipsychotica beschrijven, rapporteren ook een betere kwaliteit van leven[5]. Subjectief welbevinden is een onafhankelijke uitkomstmaat geworden in klinische studies en wordt gezien als een uitkomstmaat die relevant is voor therapietrouw en herstel. Zonder erkenning van de subjectieve ervaring van de patiënt, is een goede samenwerking in de behandelrelatie niet mogelijk[6–10].

Het overige deel van de introductie beschrijft de geschiedenis van het onderzoek naar subjectief welbevinden onder antipsychoticagebruik en de wetenschappelijke achtergrond van de onderzoeksvragen.

Box 1. Schizofrenie

Schizofrenie is een ernstige psychiatrische aandoening die ongeveer 1 op de 100 mensen treft, meestal in de vroege adolescentie begint en anderhalf keer vaker voorkomt bij mannen dan bij vrouwen. Patiënten met schizofrenie lijden aan psychoses die meestal vaker in het leven terugkeren. Tijdens een psychose hebben patiënten last van hallucinaties en wanen. Hallucinaties zijn zintuigelijke ervaringen waarvoor geen externe prikkel is (bijvoorbeeld 'stemmen' horen) en wanen zijn vaste overtuigingen, die niet stroken met de werkelijkheid (mensen kunnen het idee hebben dat ze achtervolgd worden). Vaak raakt ook het denken verstoord en krijgen patiënten moeite met plannen en organiseren. Hierdoor lukt het sommige psychotische patienten minder goed om voor zichzelf te zorgen. Sommige patienten houden cognitieve problemen na een psychotische episode en ervaren daarnaast een afname in de levendigheid van hun gevoelsleven. Hierdoor hebben mensen minder energie en zin in het aangaan van sociale contacten. Wat de behandeling en begeleiding van schizofrenie kan bemoeilijken, is dat een deel van de patienten zich niet beseft dat hun klachten veroorzaakt worden door een aandoening. Er is een genetische kwetsbaarheid voor het ontwikkelen van schizofrenie. Zo hebben kinderen met 2 ouders met schizofrenie 50% kans om zelf ook de aandoening te ontwikkelen. De precieze biologische oorzaak van schizofrenie is nog niet achterhaald.

Box 2. Antipsychotica

De wanen en hallucinaties van psychose kunnen worden behandeld met antipsychotische medicatie. Als die medicatie wordt gestopt, komen de symptomen bij 4 op de 5 patienten terug. Medicatie vermindert de verschijnselen, maar er bestaat nog geen behandeling die de aandoening geneest. Antipsychotische medicatie veroorzaakt bijwerkingen, waar sommige mensen veel last van hebben. Dat kan een reden zijn om de medicatie te staken. Antipsychotica ontlenen hun werking voornamelijk aan blokkade van de dopamine D_2-receptor, al bestaan er hypotheses dat ook bezetting van sommige serotonerge en glutamaterge receptoren daar aan bijdraagt. Overmatige bezetting van de dopamine receptoren veroorzaakt bijwerkingen, onder andere parkinsonisme, akathisie, dystonieën en seksuele stoornissen. Veel middelen binden echter ook aan anticholinerge, histaminerge en glutamaterge receptoren. Bezetting van deze receptoren kan ook bijwerkingen veroorzaken zoals gewichtstoename, duizeligheid, slaperigheid en obstipatie.

Doelstellingen van dit proefschrift

We hebben ons voor dit proefschrift als eerst gericht op strategieën om de therapeutische relatie te verbeteren en zo medicatietrouw te bevorderen. We beschrijven de ontwikkeling van de eerste keuzehulp voor antipsychotica en richten ons daarna op het beschrijven van farmacologische en psychologische factoren die het subjectief welbevinden van patiënten met een psychotische stoornis mogelijk beïnvloeden.

Hoofdstuk 1: De ontwikkeling van de Persoonlijke Antipsychotica Keuzewijzer

Dit hoofdstuk beschrijft de ontwikkeling van een website die mensen helpt bij het kiezen van een antipsychoticum. We hebben eerst een systematische literatuurstudie verricht naar de belangrijkste effecten en bijwerkingen van 15 antipsychotica die in Nederland worden voorgeschreven. We hebben de gegevens over de ernst of frequentie van een bijwerking en de sterkte van een gewenst effect geordend, er scores aan toegekend en deze scores verwerkt in een algoritme. In de keuzehulp kunnen patiënten per bijwerking en type effect aangeven hoeveel waarde ze er aan toekennen. Bijvoorbeeld: 'hoe belangrijk vind je het als je van je medicatie in gewicht zou aankomen?'. De score van deze persoonlijke voorkeuren is aan het algoritme toegevoegd. Via dit algoritme presenteert de keuzehulp een rangorde van antipsychotica die meer of minder bij de voorkeuren van de patiënt passen. Naar een deel van de bijwerkingen zijn nooit gerandomiseerde geblindeerde klinische trials verricht, waardoor we ons hebben moeten beperken tot informatie uit onderzoeken met een lagere bewijskracht. Het advies van de PAKwijzer kan daarom alleen als een keuzesuggestie gelden. Patiënten worden aangemoedigd om de uitkomst met hun behandelaar te bespreken.

We hebben de overwegingen bij de ordening en toewijzing van scores zo transparant mogelijk opgeschreven, omdat sommige beslissingen zijn gebaseerd op de klinische ervaring van experts. Zo kan de PAKwijzer geüpdatet worden als klinische inzichten veranderen of als er nieuwe antipsychotica verschijnen of nieuw onderzoek betreffende bestaande antipsychotica.

Tenslotte doen we suggesties voor vervolgonderzoek naar de effectiviteit van PAKwijzer op de kwaliteit van gedeelde besluitvorming en de therapeutische relatie. We hopen dat patiënten subjectief minder bijwerkingen ervaren als ze betrokken zijn bij de besluitvorming, zodat dit uiteindelijk de medicatietrouw bevordert.

Hoofdstuk 2: Is er een relatie tussen de dopamine D_2-receptor affiniteit van antipsychotica en subjectief welbevinden bij mensen met een psychotische stoornis?

We hebben voor de volgende hoofdstukken gegevens gebruikt van de Genetic Risks and Outcome of Psychosis (GROUP)-studie. Dit longitudinale observationele cohort bevat gegevens van patiënten, hun gezonde eerstegraads familieleden en een groep van gezonde mensen zonder eerstegraads familielid met psychotische klachten.

Sommige antipsychotica binden "strakker" aan de dopamine D_2-receptor dan anderen. Men spreekt dan van een antipsychoticum met een hogere bindings-affiniteit. Uit eerdere onderzoek zijn er aanwijzingen naar voren gekomen dat patiënten die een strak bindend middel gebruiken, zich slechter voelen dan patiënten die losser bindende middelen gebruiken. Wij vonden in het GROUP-cohort geen aanwijzingen dat de affiniteit voor de D_2-receptor samenhangt met het subjectief welbevinden en denken dat een verband nog zou kunnen worden onderzocht in een geblindeerde klinische studie of in een cohort waarbinnen patiënten lang genoeg gevolgd worden om bij hen zelf het effect van verschillende middelen te evalueren. De medicatietrouw moet dan goed worden bijgehouden.

Hoofdstuk 3: Hangt de score op de SWN-20 samen met direct gemeten dagelijkse stemmingsschommelingen?

We hebben bij patiënten en hun gezonde broers en zussen onderzocht of kortdurende negatieve gemoedstoestanden, stressgevoeligheid en een anticipatie op beloning samenhangen met het ervaren van een subjectief welbevinden. We hadden gegevens van een groep patiënten en eerstegraads familieleden die 10 keer op een dag gevraagd waren te rapporteren hoe ze zich voelden. Deze methode heet de Experiencing Sampling Methode. We hadden van deze groepen ook de subjectief welbevinden scores (gemeten met de SWN-201), die een gemiddelde van de afgelopen week vertegenwoordigen. We vonden dat mensen die zich gemiddeld op een dag vaker opgewekt, ontspannen, tevreden of enthousiast voelden, gemiddeld hoger op subjectief welbevinden scoorden. Mensen die zich gemiddeld vaker op een dag onzeker, sober, eenzaam angstig of geïrriteerd voelden, rapporteerden gemiddeld ook een lage subjectief welbevinden in de week ervoor. Deze relatie geldt voor zowel patiënten als gezonde familieleden en we vonden de relatie niet voor stressgevoeligheid of belonings-

anticipatie. We concluderen dat de SWN-20, die zich richt op het subjectief welbevinden van de afgelopen week, samenhangt met direct gemeten dagelijkse gemoedstoestanden.

Hoofdstuk 4: Hangen de persoonlijkheidskenmerken neuroticisme en extraversie samen met subjectief welbevinden?

In dit hoofdstuk hebben we willen onderzoeken of het niveau van subjectief welbevinden samenhangt met bepaalde karakterteken van patiënten. In de algemene bevolking is dat verband al aangetoond. Het gaat om neuroticisme (gevoeligheid voor negatief gekleurde emoties) en extraversie (de hang naar sociale contacten). Neuroticisme wordt gezien als een kwetsbaarheid en extraversie als veerkracht voor het beloop van de aandoening. Deze karaktereigenschappen worden in kaart gebracht met een vragenlijst, de Neuroticism-Extraversion-Openness-Five Factory inventory. Met een longitudinale studieopzet wilde we achterhalen of neuroticisme en extraversie voorspellers zijn voor het beloop van het subjectief welbevinden over 6 jaar. We maten dit bij zowel patiënten als gezonde mensen.

Eén op de 7 patiënten houdt gedurende zes jaar een laag subjectief welbevinden (score onder de 80, op een schaal van 60-120) en deze groep scoorde gemiddeld hoger op neuroticisme en lager op extraversie. Het effect van neuroticisme en extraversie bleef bestaan nadat we voor de psychotische en depressieve symptomen hadden gecorrigeerd. Mensen die hoog scoren op neuroticisme zijn gevoeliger voor angst-gerelateerde en depressieve klachten. We concludeerden dat neuroticisme daarmee een belangrijke karaktertrek is bij de start van een behandeling. Mogelijk kunnen interventies gericht op neuroticisme het beloop verbeteren.

Hoofdstuk 5: Is er een relatie tussen coping en negatieve life events en subjectief welbevinden?

'Coping' verwijst naar de manieren waarop we gedragsmatig en cognitief proberen stress te voorkomen, te hanteren of te verlichten. In dit hoofdstuk hebben we bij patiënten eerst onderzocht of negatieve levensgebeurtenissen in de afgelopen 3 jaar in verband stonden met een slechter subjectief welbevinden en daarna gekeken of deze relatie werd beïnvloed door de copingstijlen die

mensen toepassen. Dit heeft geleid tot een statistisch model dat de samenhang beschrijft. Dit zogenaamde mediatiemodel hebben we daarna ook op gezonde broers en zussen toegepast.

We vonden dat mensen die proactiviteit en het zoeken van sociale steun toepasten, vaker een hoger subjectief welbevinden rapporteerden. De eerstegraads familieleden pasten die coping vaker toe dan patiënten. We vonden daarnaast dat de relatie tussen negatieve levensgebeurtenissen en subjectief welbevinden, die bij de broers/zussen negatief was, verklaard werd door het gebruik van passieve coping. Het is nog niet zeker of mensen die passieve coping stijlen gebruiken, vatbaarder zijn voor negatieve gebeurtenissen (zoals je baan verliezen) of dat de impact van die levensgebeurtenissen op het subjectief welbevinden groter wordt als je er passief mee omgaat. Onze bevindingen sluiten aan bij de bevindingen van eerdere studies[11–14].

Onze bevindingen suggereren dat patiënten met een psychotische stoornis er van zouden kunnen profiteren als hun behandeling zich richt op de versterking van hun coping strategiëen.

Algemene conclusie

We hebben met de ontwikkeling van de PAKwijzer de eerste online keuzehulp voor antipsychotica gemaakt die rekening houdt met de voorkeur van de patiënt. Onder andere omdat voor bepaalde onderdelen maar beperkte wetenschappelijke bewijsvoering beschikbaar was, vervangt de PAKwijzer niet het klinische consult. Maar hij kan patiënten betrekken bij de keuze van een antipsychoticum, waardoor ze hopelijk minder last van de bijwerkingen ervaren. We hebben de keuzehulp ook gemaakt in de hoop dat de kwaliteit van de therapeutische relatie verbetert en patiënte zich wat steviger voelen. Toekomstig onderzoek moet nog uitwijzen of dat zo is.

Met behulp van het GROUP-cohort, hebben we in de overige hoofdstukken onderzoek gedaan naar verschillende farmacologische en psychologische factoren die het subjectief welbevinden beïnvloeden van patiënten met een psychotische stoornis. Als eerste vonden we onvoldoende bewijs om te kunnen zeggen dat de receptorbindingsaffiniteit van een antipsychoticum leidend moet zijn bij de keuze van een antipsychoticum om het subjectief welbevinden te verbeteren.

De SWN-20, de meest gebruikte vragenlijst die subjectief welbevinden bij patienten meet, lijkt voldoende samen te hangen met kortdurende gemoedstoestanden om te kunnen zeggen dat een ecologische valide meetinstrument is, dat bovendien makkelijk te gebruiken is.

We vonden dat één op de 7 patiënten een laag subjectief welbevinden blijft houden gedurende 6 jaar. Hoewel we correlaties hebben onderzocht en geen oorzakelijke verbanden, vonden wij wel aanwijzingen dat neuroticisme als karaktertrek een risicofactor vormt voor een slecht subjectief welbevinden, ongeacht of iemand psychotische of depressieve klachten heeft of een antipsychoticum gebruikt. We vonden ook dat actieve coping stijlen bijdragen aan een beter subjectief welbevinden bij patiënten met een psychotische stoornis. Daartegenover staat dat een passieve houding met betrekking tot negatieve levenservaringen het subjectief welbevinden lijkt te verslechteren. Hoewel daar nog onderzoek naar verricht moeten worden, zou het subjectief welbevinden van patiënten met een psychotische stoornis misschien verbeterd kunnen worden met psychotherapeutische interventies die zich richten op copingstijlen en persoonlijkheidskenmerken.

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Portfolio

Name	Floor A. van Dijk
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PhD-period	September 2014 - July 2019
Promotor	Prof. Lieuwe de Haan
Co-promotor	dr. Frederike Schirmbeck
Other members	Prof. Dieter Naber, Prof. Iris Sommer, Prof. Mirjam Sprangers, dr. Pelle de Koning, dr. Lindy-Lou Boyette

Publications

Peer reviewed – in this thesis

2019 van Dijk FA, Schirmbeck F, Boyette L-L, de Haan L. Coping styles mediate the association between negative life events and subjective well-being in patients with non-affective psychotic disorders and their siblings. *Psychiatry Research* 2019;272

2017 van Dijk FA, Schirmbeck F, Haan L de. A longitudinal analysis of the effects of neuroticism and extraversion on subjective well-being in patients with schizophrenia. *Psychiatry Research* 2018;259 (September 2017):538-544..

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2017 van Dijk F, de Wit I, Blankers M, Sommer I, de Haan L. The Personal Antipsychotic Choice Index: Introducing a Tool for Shared Decision-Making in Selecting Antipsychotic Medication. *Pharmacopsychiatry* 2017

Peer reviewed – others

2019 Swets M, van Dijk FA, Schirmbeck F, et al. Patterns of obsessive-compulsive symptoms and social functioning in schizophrenia; a replication study. *Psychiatry Research* 2019;27

PhD Training

General courses

2016 Practical Biostatistics

(International) conferences – orals/presentations

2017 Programme of psychosis, Science in Arkin, so what?
Oral presentation: *subjectief welbevinden en persoonlijkheids-kenmerken*

2017 NVvP Voorjaarscongres (VJC), Maastricht
Poster presentation: *Een analyse van het effect van neuroticisme en extraversie op het subjectief welbevinden over 3 jaar bij patiënten met schizofrenie*

Other

2019 NVvP VJC, Maastricht

2019 Congres Nederlandse Vereniging voor Groepsdynamica en psychotherapie

2018 6th Biennial Schizophrenia International Research Society Conference, Florence

2016 NVvP VJC, Maastricht

2015 Annual Meeting, American Psychiatric Association, Toronto

2015 NVvP VJC, Maastricht

Teaching

2017 Supervising
N. de Leeuw, Master thesis Research project Clinical Psychology, VU Amsterdam. *The influence of personality on subjective well-being in psychotic patients, when adjusting for medication adherence*

2017 Lecturing and tutoring
Ten working classes for 24 third year medical students (University of Amsterdam), educating major topics of psychiatry

2016 Lecturing
Clinical lecture (Klinisch lijn onderwijs) for 3rd year medical students (UvA). *The depressed patient*

2014 Lecturing
Class on medical skills (Vaardigheidsonderwijs) for 30 third year medical students (UvA) *The psychiatric examination*

Clinical work and education

2006 – 2013
Medical school, University of Amsterdam

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Residency of psychiatry in Academical Medical Centre, Arkin GGZ and Zaans Medisch Centrum

2017 Basic Course Groupdynamics

2018 Basic Course Mentalization Based Treatment
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About the author

Floor van Dijk was born on the 10th of June 1987 in Utrecht. She obtained her gymnasium diploma at the St. Bonifatius college Utrecht in 2005. After a year of working and volunteering in Benin (West Africa), she moved to Amsterdam in 2006 to study medicine at the Academical Medical Centre/University of Amsterdam. In 2013 she completed her medical degree with distinction (cum laude) with an elective clerkship in psychiatry and a final clerkship in internal medicine. She decided to specialize in psychiatry. She worked a year as a physician (ANIOS) at the Mentrum clinic Eerste Constantijn Huijgensstraat and started working on de development of the Personal Antipsychotic Choice Index for prof. Lieuwe de Haan in 2014. In the same year, she started her training as a psychiatrist in the Academic Medical Center (now: Amsterdam UMC, location AMC). She contintued doing research on the side, this time into the subjective well-being of people with schizophrenia with data from the GROUP cohort. As a resident, she worked for two years in the AMC, then worked at the psychiatric emergency service of Arkin (ABT Noord) and finished her residency by working a year at the Zaans Medisch Centrum on the department for psychiatric psychotherapy. During her studies, she attacked hurdles on the 100m track, learned to dance forró and eventually picked up singing. From July 1st 2019 on she will be working as a psychiatrist at the Antoni van Leeuwenhoek hospital.
Floor lives together with Marten in Amsterdam.

Dankwoord

Hoera, het is af! Ik wil heel graag wat mensen bedanken die op allerlei manieren mijn promotieonderzoek hebben mogelijk gemaakt.

De data was al verzameld toen ik aan mijn onderzoek begon en tot mijn spijt heb ik nooit een deelnemer van het GROUP-cohort ontmoet. Indachtig de vele mensen met psychose die ik in mijn klinische werk ben tegengekomen, gaat mijn dank uit naar alle patiënten, hun familieleden en gezonde deelnemers die lange dagen in het AMC hebben doorgebracht om vragenlijsten te beantwoorden en testtaken uit te voeren. Zonder hun bereidwilligheid was het niet gelukt.

Prof. dr. de Haan, beste Lieuwe. Ik heb je aan je mouw getrokken tijdens een promotie omdat ik graag 'onderzoek wilde doen'. Bedankt dat me direct uitnodigde en ook nog enthousiasmeerde met je geestigheid (Over de PAKwijzer: 'WEET je wat we doen als titel! Ranking the Stars. Ja dit wordt leuk hoor' — maar die kwam niet door de academische ballotage van het publicatieproces). Met de de PAKwijzer heb ik onschatbare kennis opgedaan voor de klinische praktijk. Ik bewonder je kalme opgewektheid en scherpe analytische vermogen. Je weet altijd de rode lijn te bewaken en ik heb inspiratie opgedaan van de helderheid waarmee je presentaties geeft.

Dr. Schirmbeck, beste Frederike. Ik had me geen fijnere copromotor kunnen wensen. Ik ben blij dat ik een stukje van je teamspirit en betrokkenheid heb mogen meekrijgen. Bedankt voor je vriendelijke vasthoudendheid, de hulp bij statistische vraagstukken en scherpe bevraging van de redeneringen in mijn papers. Erg leuk dat we daarnaast nog gefilosofeerd hebben over het nut van bedenken wat er op je grafsteen moet staan en hier en daar een wijntje.

Nicole, zonder jouw lag er geen proefschrift. Bedankt voor je opgewekte hulp in de aanloop naar de verdediging, je hebt me praktische dingen uit handen genomen en dat heeft mijn zenuwen getemperd.

Medeonderzoekers van de Vroege Psychose en de rest van de 3e verdieping; maar een paar man sterk waren we in mijn onderzoeksjaar, maar we hebben standgehouden, zelfs op een Goede vrijdag. Beste Iris, dankzij jou organisatievermogen kwam ons PAKwijzerartikel op tijd af. Leuk om een gezamenlijke drive te hebben om ons werk zo goed mogelijk te doen. Natascha, knap hoe je

je masterthesis in korte tijd hebt geschreven en leuk om te zien hoe je ingebed raakte in de onderzoeksgroep. Beste Ellen en Dieuwke, met jullie enthousiasme en humor maakten jullie de sfeer op onze gang.

Jentien, ik heb bij jou aanschouwd hoe politiek en bestuurskunde dienen te worden bedreven. Ik kijk op tegen je onderzoeksvolharding en ben trots dat ik je bokservaring heb weerstaan op een zeker feestje. Heel leuk dat we interesse voor het vak delen. Geeske, ik heb me gelaafd aan je levenslust en het belang dat je hecht aan goed getimede koffie. En lieve Marije, wat hadden wij het goed in ons onderzoekskamertje. Je was een grote relativering ten tijde van stress met ons fantaseren over de wetenschappelijke tijdschriften waarop we een abonnement zouden nemen (want dat doet het zo goed op feestjes). Dank voor het plezier en, zo vaak, het luisterend oor.

Leden van de promotiecommissie; prof. dr. D. Naber. Your pioneering publications on subjective well-being in psychotic disorders have formed the basis of this thesis. It is an honor to have you on the evaluation committee. Prof. dr. I. Sommer, prof. dr. M. Sprangers, dr. L.L. Boyette, dr. P. de Koning, van harte bedankt voor het lezen en beoordelen van mijn proefschrift. Dr. A. Lok, bedankt voor het opnemen van de oppositie.

Omdat ik het grootste deel van mijn onderzoek tijdens de opleiding tot psychiater heb verricht, is het gevoelsmatig verbonden met het toch al niet eenvoudige proces van psychiater worden. Heel veel dank aan alle collega's van uiteenlopende disciplines (dat het werken in dit vakgebied zo leuk maakt) — van het AMC, Arkin en het Zaans Medisch Centrum — zonder jullie was dat niet gelukt. Ik noem in het bijzonder mijn opleiders, supervisoren en werkbegeleiders, Margje Jalink, Marloes Oudijn, Arjen Sutterland, Jitschak Storosum, Anja Lok, Jan Stoker, Pelle de Koning, Laura van Groenendaal, Uli Ziegler en Dorien Philipszoon; onwijs bedankt voor het tonen dat plezier in en om het contact met onze patiënten cruciaal is voor goede zorg, voor de camaraderie op de werkvloer, het laten zien hoe je cohesie in een team (of therapiegroep) bewerkstelligt, het geduld als ik 10 overwegingen per patiëntencasus had en de bereidwilligheid om daarna nog iets over jezelf te vertellen, het overbrengen van veel kennis in korte tijd, het oppakken van opleidingstaken en tenslotte de incidentele rust & wijsheid.

Lieve Pim Scholte, de eerste stapjes in de wereld van psychotherapie zette ik dankzij jou al voor mijn coschappen bij Equator. Je werd mijn mentor en aanjager. Dank dat ik me aan je mocht optrekken en voor alle gezelligheid.

Lieve assistentengroep van het AMC en in het bijzonder mijn lichting Maarten, Hester en Nienke: gedeelde smart is halve smart. Samen hebben we geprobeerd het beste te maken van de vele opleidingseisen die op ons afkwamen en ik denk dat ons dat heel goed is gelukt. Dank voor de steun, de gezellige borrels en aiosweekendjes, het nauwe samenwerken in moeilijke casussen, het vertrouwen in mij toen ik voorzitterstaken deed en niet vergeten de Sinterklaasgedichten (frustratie alom dat ik nooit heb achterhaald wie dat deed!). Ik vind het onwijs fijn dat het zowel hilarisch is als vertrouwd voelt wanneer we elkaar zien en ik hoop dat we dat blijven doen in de toekomst.

Lieve leden van mijn APO-groep: een deel van ons is al psychiater en een deel heeft om goede redenen wat vertraging opgelopen. We hebben ons door boeiende maar soms erg trage onderwijsochtenden heen geslagen; dank voor de opwarmende relativering als ik dan weer eens in diepe academische vertwijfeling verkeerde. Thijs, Jeichien, David en Maurits: ik hoop dat we nog vaak een Arkin-AMC huis huren en ronddwarrelen in een Maastrichts cafe tijdens het Voorjaarscongres.

En leuke aiossen van het ZMC: wat een belevenissen en plezier hebben we gehad op de Dagkliniek. Bedankt voor alle gezelligheid en jullie steun en adviezen bij het zoeken naar een baan.

Intervisiegenoten Ilja, Geeske, Lisa, Maja, Maria en Ati: dank dat jullie mijn behoefte aan structuur de ruimte geven, haha! Etentjes met jullie bieden een zee van herkenning en ook nog gezelligheid. Heel leuk dat we allemaal belang hechten aan wetenschappelijke verdieping; jullie houden mijn ambities scherp.

Lieve Spaansekraag; Marieke, Linda, Floor, Berthe, Rianne en Marjolein: bij jullie kan ik de acute stress van ons werk & het leven kwijt met het vertrouwen dat ik er warme steun en aanmoediging voor terugkrijg. Ik ben onwijs blij met jullie.

Lieve Utrechters: wat komt er veel goeds voort uit een gedeelde middelbare schooltijd. Ik ben ongelooflijk blij dat we elkaar nog zien en baal ervan dat we niet (meer) bij elkaar in de buurt wonen.

Lieve Myrthe, je was er bij toen ik afstudeerde en vergezelde me naar een geneeskundecongres terwijl je muzikant bent. Ik ben jaloers op je vermogen om te kiezen voor wat goed voor je is en ben heel trots op je succes.

Lieve Simone, wijntjes met jou zijn een verdiepend feestje. Dank voor je royale relativeringsvermogen. Onwijs leuk dat je een (zeer gewaardeerde!) summerschoolclass hebt gegeven in het AMC en iets van mijn werkzame leven hebt willen aanschouwen.

Lieve Yasmin, je ging me voor in promoveren en hebt me met je humor en openhartigheid heel vaak bijgestaan. Ik had het geluk om met je in hetzelfde co-groepje te belanden en ben heel blij dat je ook naar het AMC gekomen bent om de opleiding tot psychiater te gaan doen.

Mijn paranimfen Thijs en Rianne: lieve Thijs, wat een feest om met je te discussiëren over het vak. Je miste me toen ik op vakantie was; ik mis het leven in onze onderzoekskamer. Ik geniet van je passie voor ongeveer alles en ook zeer van de imitaties van Abe en Hidde. Lieve Rianne, studiegenoot, reisgenoot, mede-aios en nou mede-psychiater (de lijst is langer). Godzijdank hebben we al meer dan 10 jaar dezelfde interesses. Je bent zowel mijn soulmate als scherpste criticus en bent daarmee de liefste om tegenop te kijken.

Lieve familie van Dijk & Griffioen, mijn basis ligt bij jullie. Jeroentje, ik ben erg trots op je en ik vind het heel fijn dat we nog altijd in dezelfde stad wonen. En Judith, sinds jij er bij bent, is het nog gezelliger. Laten we nog heel vaak samen eten en borrelen. Lieve Gerdien en Hans, van jullie kreeg ik levenswijsheid, mededogen en reislust mee. Zonder de thuisbasis in Utrecht en jullie betrokkenheid op de achtergrond was dit hele boekje er niet gekomen. Hetty en Toon, wat zijn jullie leuke schoonouders. Ik geniet van de gezelligheid bij etentjes aan de grote tafel in Deventer en bedankt voor jullie vanzelfsprekende aanmoediging bij de stappen in mijn carriere. Bart, schoonbroer in Taiwan, wat was het leuk om je op te zoeken. Ik kijk uit naar een dissertatie van jouw hand en hoop dus dat je die niet in het Chinees zult schrijven.

Lieve Marten, ik vind je al zo lang lang de leukste. Het leidde geen twijfel dat je van dit boek iets prachtigs zou maken. Maar dank voor het laten varen van je bescheidenheid toen je er op stónd dat je zou meedenken over iets inhoudelijks. Met een grote glimlach denk ik terug aan de brainstormsessie voor de titel, omdat ik toen ervaren heb dat er mooie dingen onstaan als ik de leiding eens aan jou over laat. Ik hoop dat je me nog heel vaak stop wil zetten en aan de hand wil nemen, de rest van ons leven.