Optimising antipsychotic prescribing in schizophrenia

Understanding the factors contributing to antipsychotic polypharmacy and personalising treatment to improve pharmacotherapy

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Secteur des sciences de la santé

“Perfection is achieved, not when there is nothing more to add, but when there is nothing left to take away.”

– Antoine de Saint Exupéry

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SUMMARY

Schizophrenia is one of the most severe psychiatric illnesses, and affects about 1% of the world's population. Antipsychotics are the only drugs currently registered for its treatment. Antipsychotic polypharmacy (APP), the simultaneous use of two or more antipsychotics by a patient, is common worldwide for the treatment of schizophrenia, although its superior efficacy over antipsychotic monotherapy is not supported by high-quality evidence. Worse, patients on APP experience poorer outcomes than those on antipsychotic monotherapy. However, its exact prevalence in Belgium remained unknown. As part of this project, our first observational study in 6 Belgian hospitals revealed that about half of patients admitted to hospital with acute decompensation of schizophrenia were on APP, and that this proportion even increased at discharge to reach about 60%. The prevalence of antipsychotic deprescribing during psychiatric hospitalisation, i.e. reducing the number of antipsychotics, was also unknown and could benefit from comparison with data from Canada, which is a leader in deprescribing policies. Our second observational study revealed that more than twice as many patients were deprescribed after psychiatric hospitalisation in a Québec hospital than in the Belgian hospitals included. Moreover, significantly more patients in the Canadian hospital than in Belgian hospitals were switched from APP to antipsychotic monotherapy. Then, as the opinions of Belgian psychiatrists on APP was unknown, as were the elements likely to influence it, we carried out a survey. First, a scale designed to measure the social capital (i.e. the support an individual can access through their relationships and the strength of the link by which it is accessed) of psychiatrists was developed and validated for the use in the survey. Subsequently, the survey of Belgian psychiatrists revealed that psychiatrists with lower social capital were more likely to have a more evidence-based attitude toward antipsychotic polypharmacy, but that the intrinsic evidence-based medicine orientation did not affect this. Furthermore, various factors may influence the severity of symptoms and the response to antipsychotics, which may precipitate the use of APP. Among the environmental factors known to affect symptom severity, caffeine withdrawal has been little studied. Our cross-sectional study showed that the withdrawal of caffeine inside a psychiatric hospital was significantly associated with higher Global Assessment of Functioning scores at discharge and shorter hospital stays. Finally, we conducted a multisite pharmacogenetic study on patients with schizophrenia taking olanzapine and admitted to psychiatric inpatients units. We aimed at evaluating the impact of genetic polymorphisms of pharmacogenes on olanzapine plasma concentration, and their potential influence on patient outcomes. This last study revealed that conducting therapeutic drug monitoring and pharmacogenetic tests is challenging in clinical routine, which may hinder their use in routine psychiatric clinical practice, despite their potential to detect subtherapeutic plasma concentrations and/or variants that may explain poor treatment response. Altogether, our different studies indicate that (i) APP is still frequently prescribed in Belgium despite lack of

evidence-based benefits, (ii) Antipsychotic deprescribing is feasible because it is already performed in identifiable patients and situations (iii) Deprescribing and the use of antipsychotic monotherapy is still perceived in Belgium as an innovation that will have difficulty penetrating dense networks (iv) Reducing access to caffeine within a psychiatric hospital is associated with better patient functioning and shorter hospital stays (v) Carrying out therapeutic drug monitoring and pharmacogenetic testing in everyday psychiatric clinical practice in Belgium is a challenge, but enables the detection of out-of-range plasma concentrations of olanzapine, which have an impact on patient outcomes.

This project paves the way for future implementation studies aimed at deprescribing antipsychotics to achieve antipsychotic monotherapy, with the help of therapeutic drug monitoring and pharmacogenetics.

ABBREVIATIONS

AS	Activity score
ASD	Autism spectrum disorder
BPRS	Brief Psychiatric Rating Scale
C/D	Concentration/dose ratio
CGI	Clinical Global Impression scale
CI	Confidence Interval
CNV	Copy number variants
CPIC	Clinical Pharmacogenetics Implementation Consortium
CRP	C-reactive protein
CRS	Clozapine-resistant schizophrenia
CYP	Cytochrome P450
DPWG	Dutch Pharmacogenetic Working Group
DRD2	Dopamine D_2 receptors
DSM-III-R	3rd revised edition of the Diagnostic and Statistical Manual of Mental Disorders
DSM-5	Diagnostic and Statistical Manual of Mental Disorder, 5th edition
ECT	Electro-convulsive therapy
EFA	Exploratory Factor Analysis
EPS	Extrapyramidal symptoms
hERG	Human ether-a-go-go-related gene
HR	Hazard Ratio
HTR2C	5-HT_{2C} receptors
GAF	Global Assessment of Functioning scale
GMS	Glycine Modulatory Site
GWAS	Genome-wide association study
ICC	Intra-class correlation
IM	Intermediate Metabolisers
IQR	Interquartile Range

ISSP	International Social Survey Programme
ITC	Item-total correlation
KMO	Kaiser-Meyer-Olkin
LSD	Lysergic acid diethylamide
NNH	Number needed to harm
NNT	Number needed to treat
NM	Normal Metabolisers
PANSS	Positive and Negative Syndrome Scale
PET	Positron emission tomography
PM	Poor Metabolisers
PRS	Psychopathology rating schedule
RG	Resource Generator
RG-Psy	Resource Generator for Psychiatrists
RG-UK	Resource Generator UK
RTC	Randomised controlled trial
SNRI	Serotonin-noradrenaline reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
SUD	Substance use disorder
TDM	Therapeutic drug monitoring
TRS	Treatment-resistant schizophrenia
UM	Ultra-rapid metabolisers
UGT	UDP-glucuronosyltransferases
URS	Ultra-resistant schizophrenia
VTA	Ventral tegmental area

BACKGROUND

1. SCHIZOPHRENIA

1.1. EPIDEMIOLOGY

Schizophrenia was first described in 1896 by Emil Kraeplin under the term dementia praecox[1,2]. It is one of the most severe psychiatric illnesses that affects the overall functioning of patients in their daily life. The stigma associated with the disease and the high risk of relapse make it difficult to maintain employment or relationships, leading to social isolation[3].

Between 0.7 and 1% of the population in all countries suffers from this disease, which affects slightly more men than women[4]. The peak incidence occurs in late adolescence and early adulthood (Figure 1)[4]. The onset of schizophrenia before 18 (i.e. early-onset)[5-7] or during childhood (i.e. before the 13th birthday)[7] is infrequent, and associated with poorer outcomes[8]. The prevalence of these early forms is difficult to establish due to their rarity, but is estimated at up to 0.17% for early onset and about 0.04% for childhood onset[6,8]. Although the onset may be abrupt, many individuals appear to have had prodromal symptoms and a gradual development of schizophrenia[9]. Conversely, approximately 15% of individuals with schizophrenia experience onset after the age of 40 (i.e. late onset schizophrenia) and even at age 60 or older. The latter form, commonly referred to as very late-onset schizophrenia, is also sometimes described as a persistent persecutory state, or late paraphrenia, and is somewhat more common in women[10]. Like patients with early-onset schizophrenia, those with a late onset have poorer psychopathological status and cognitive and functional abilities than other patients[10].

Schizophrenia is a leading contributor to disease burden, and despite its relatively low incidence, remains one of the top 20 causes of disability (i.e. 12th most disabling) among the 310 diseases and injury worldwide[11].

Schizophrenia accounts for about 2% of health care expenditure in Belgium, which is 10 times the cost of an average citizen. These health costs are due to hospitalisation, followed by outpatient care, medication and residential

facility. However, the highest personal contribution of these patients concerns their medication (31.6%), followed by physician visit and hospitalisation, with antipsychotics representing the highest personal expenditure of all psychotropic drugs[12].

In addition to the cost of healthcare (i.e. direct cost), the economic impact of schizophrenia is also due to unemployment, loss of productivity of patients and their families or other informal carers (friends, neighbours) and social welfare costs (indirect cost). The cost of informal care is higher than the cost of productivity lost by the patient, with most severely ill and less functioning patients having higher indirect costs than patients with milder symptoms.[13] Due to the age of onset and early mortality of people living with schizophrenia, 70.8% of schizophrenia cases occur in the 25-54 years group[11]. The economic burden/deficit of schizophrenia is also the greatest in this age group, as this is when individuals are the most likely to be economically productive[11].

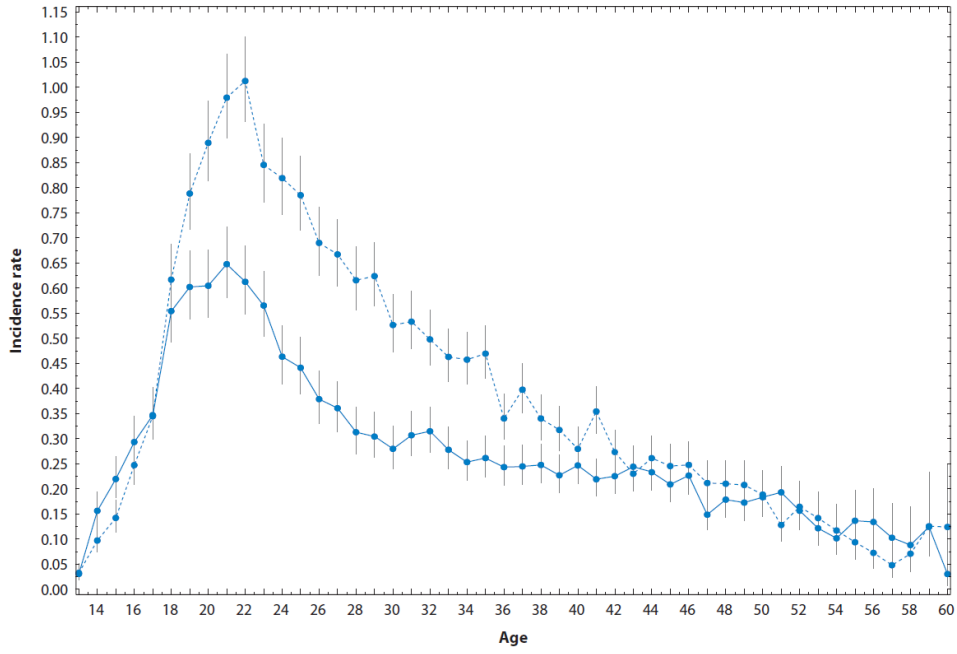

Figure 1. Incidence of schizophrenia among men (dotted lines) and women (solid lines) per 1000 years. Extracted from Laursen et al. 2014 [4]

1.2. GENETICS OF SCHIZOPHRENIA AND ENVIRONMENTAL INTERACTIONS

Twin studies conducted in the last century first showed that schizophrenia is a heritable disorder[3]. This heritability, estimated at 60 to 80%, was confirmed by the first genome-wide association study (GWAS), which identified more than 100 loci associated with the disease[14], confirming that schizophrenia is a polygenic disorder. Single nucleotide polymorphism (SNP)-based heritability is estimated at 24%[15], which is lower than the heritability, as it only captures the variance associated with the common SNPs measured in the GWAS[15]. Of the variants identified as being associated with schizophrenia, approximately 75% are protein-coding genes, and 8% are within 20kb of a gene. However, most of the associated variants affect protein expression rather than structure[14]. The variants involve genes coding for dopamine D2 receptors, confirming the most commonly accepted aetiology of schizophrenia, but also genes involved in the glutamatergic pathways, the second leading contender of schizophrenia[14]. Although most of the heritability of schizophrenia is attributed to common variants, some rare variants (rare copy number variants (CNV) or rare coding variants) have been shown to be strong risk factor for schizophrenia[15].

More recently, robust evidence demonstrates an overlap between CNV of schizophrenia and of intellectual disability[16] and autism spectrum disorder (ASD), providing insight into the cognitive symptoms of schizophrenia. Indeed, the deletion at 15q11.2 is for example strongly associated with schizophrenia and is a major cause of the Prader Willi syndrome[16].

A new GWAS published in 2022 identified 287 loci associated with schizophrenia[15], improving the comprehension of the biology of the disease. Variants have also been identified in genes coding for receptors and ion channels, mostly post-synaptic, such as voltage-gate calcium (CACNA1C) and chloride channel, metabotropic glutamate (GMR1) and GABA (GABBR2) and the NMDA ligand-gated subunit GRIN2A. Other genes encode proteins that have multiple functions such as synaptic organisation, differentiation and

transmission. This study also confirms the overlap with rare variants involved in ASD and neurodevelopmental disorders[15].

In addition, environmental factors may interact with genetic factors to modulate the risk of schizophrenia, but their interaction is not fully understood. Furthermore, it is not clear whether all environmental factors are risk factors or consequences of genetic variants. For example, obstetric complications are associated with an increased risk of schizophrenia, but it is possible that schizophrenia risk variants increase the risk of obstetric complications, as certain genes are expressed in the placenta, leading to a disruption of brain development. Conversely, living in a densely populated city and migration are thought to increase the risk of developing the disease through an aberrant stress-response circuit, leading to sensitization of the dopamine system[17]. Childhood adversity has been shown to be strongly associated with schizophrenia (OR=2.87, 95% Confidence Interval (CI)= 2.07-3.98)[17], but some caution should be exercised as these results emerged from retrospective studies based on self-reporting, and therefore subject to recall bias. This recall bias is confirmed by studies comparing retrospective measures of childhood trauma with prospective ones from official records, highlighting a low level of agreement. Finally, although there has been considerable debate about whether the association is causal or not, recent findings show that cannabis use increases the risk of developing schizophrenia by a factor of four[18], and that heavy consumers have an even higher risk, suggesting a dose-dependent effect[19].

1.3. PATHOPHYSIOLOGY

The discovery of these genetic variants is improving our understanding of the pathophysiology of schizophrenia. In addition to these genetic studies, neuroimaging provides further insight into the condition. Neuroanatomical abnormalities have been found in individuals with schizophrenia, such as general thinner cortex and a reduced surface area, particularly in the frontal

and temporal lobe regions. Early onset, longer duration of illness and more severe positive and negative symptoms are associated with even greater thinning of the cortex. Smaller surface area is thought to be due to early neurodevelopmental processes, likely genetic, while volume decline overtime may better reflect cortical thinning due to neurodegenerative and environmental factors[20]. In addition, a smaller intracranial volume was found in patients with schizophrenia compared with controls. As a final intracranial volume is reached by the age of 14, this supports the hypothesis of an early disruption of neurodevelopment in people with schizophrenia[21].

Neurodevelopment is characterised by the production of synaptic connections, but also by the pruning of synapses as part of the maturation process, so that an adolescent has half as many synapses as a child. In schizophrenia, these processes are disrupted at an early stage, resulting in impaired neuronal communication and cognitive impairement[17]. As a consequence, abnormal signalling is observed in the brains of individuals with schizophrenia, especially excitatory-inhibitory imbalance in the prefrontal cortex[22]. Alteration in GABA synthesis, but also abnormalities in NMDA receptor function and glutamatergic signalling are thought to cause this inbalance[17], which has been confirmed by the recent genetic studies as mentioned above[15]. This imbalance will eventually lead to an alteration in gamma oscillation and thus in the coordination of brain functions[17], resulting in irregularities in neural networks, which are supposed to be responsible of the negative and cognitive symptoms of schizophrenia[23].

Besides these findings, the main cause of the psychotic symptoms identified to date in schizophrenia is the alteration of dopamine transmission in several areas of the brain. The dysregulation of dopamine pathways was first suggested by the discovery of the first antipsychotic, chlorpromazine[24], and subsequent understanding that antipsychotics act by binding to the dopamine D2 receptors[25], and more specifically by blocking these receptors[26]. Post-mortem studies first suggested that people with schizophrenia had a higher density of these receptors. However, in vivo positron emission tomography (PET) studies failed to confirm this hypothesis.

These results led to a second hypothesis, suggesting that the symptoms of schizophrenia were due to an increase in dopamine transmission, rather than a greater D2 receptors density, and that the increased number of receptors found in post-mortem studies was mainly due to long-term treatment with antipsychotics[27]. To confirm this second hypothesis, amphetamine-induced dopamine release assays were conducted in schizophrenic patients, and showed that the administration of amphetamine, which stimulates dopamine transmission, worsens the positive symptoms of these patients[27]. To elucidate the pathogenesis, PET studies were performed on patients in the prodromal phase of schizophrenia and compared to a control group and to patients with schizophrenia. The advantage of studying patients in prodromal states is to avoid the possible effect of antipsychotics on dopaminergic pathways. A positive correlation was found between the severity of the prodromal symptoms and the level of dopamine uptake in the striatum, which was even higher in patients with schizophrenia. These results suggest an increase in subcortical dopamine activity, even before the full onset of schizophrenia[28]. A meta-analysis clarified the nature of dopaminergic dysfunction by showing an increase in dopamine synthesis and release from presynaptic neurones, without an increase in neuron density or postsynaptic receptors[29].

Dopaminergic neurons are mainly located in the ventral tegmental area (VTA), the substantia nigra of the brain and the arcuate nucleus of the hypothalamus (Figure 2)[30]. Neurons of the substantia nigra project mainly to the dorsal striatum (i.e. the nigrostriatal pathway) and are involved in motor function and learning. Neurons of the VTA project to the prefrontal cortex via the mesocortical pathway and to the nucleus accumbens via the mesolimbic pathway[30], where they play a role in reward and motivation. The last dopaminergic pathway lies between the hypothalamus and pituitary gland and regulates prolactin secretion[30]. The dopaminergic pathway most affected in schizophrenia is not clearly defined, but it has recently been suggested that it may be the dorsal rather than the limbic subdivision of the striatum[31].

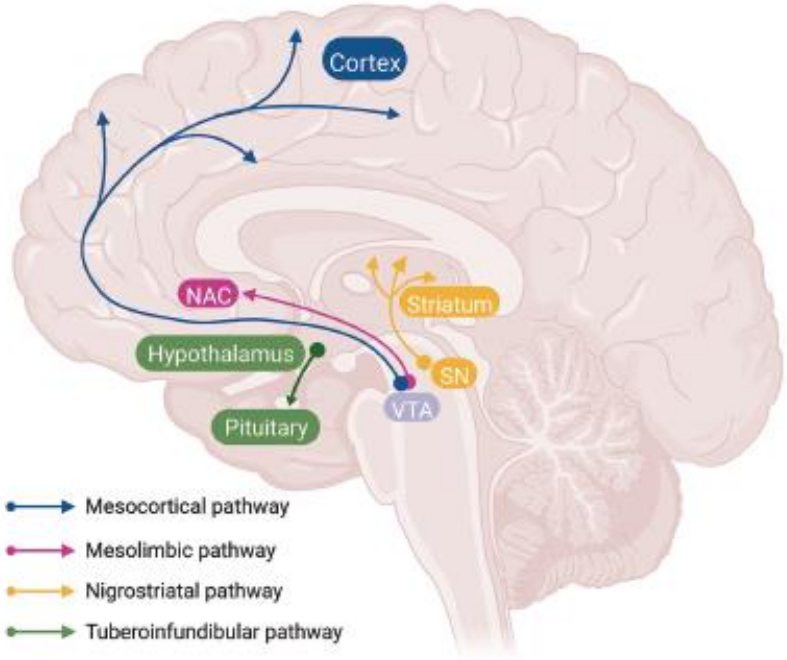

Figure 2. Dopaminergic pathways. Extracted from Xu H. & Yang F. (2022)[30]

Nevertheless, hyperdopaminergic transmission in the mesolimbic pathway (i.e. from the VTA to the nucleus accumbens) induces positive symptoms such as delusions and hallucinations[30,32], while hypodopaminergic transmission in the mesocortical pathway (i.e. from the VTA to the prefrontal cortex) and thus hypodopaminergic function in the frontal lobe causes negative and cognitive symptoms[23], which is confirmed by PET imaging studies[30].

These findings demonstrate that dysregulation of dopaminergic pathways is probably the final common pathway of psychosis, but what drives this dysregulation is not fully elucidated. Glutamatergic dysfunction has recently emerged as a major cause of dopamine dysregulation, a hypothesis supported by the genetic studies mentioned above.

The glutamate hypothesis emerged with the observation of schizophrenia-like but not identical psychotic and dissociative effects of NMDA antagonists

such as PCP ("angel dust") or ketamine[17,23,33]. Later, a reduced concentration of glutamate was observed in the cerebrospinal fluid of individuals with schizophrenia[33]. The main hypothesis commonly accepted is that hypoactivity of NMDA glutamate receptors on GABA interneurons lead to overactive glutamate downstream pathways, over-stimulating the mesolimbic dopaminergic pathway in the VTA (Figure 3)[32]. Pharmacologic studies support this hypothesis, in particular the administration of glycine (i.e. an agonist in the glycine modulatory site (GMS) of the NMDA receptors) improves positive, negative and cognitive symptoms in patients with schizophrenia[33]. However, negative and cognitive symptoms seem to be better improved by NMDA agonists than the positive symptoms[23]. Nevertheless, glutamate is certainly involved in the pathophysiology of schizophrenia and it is interesting to note that glutamatergic receptors are involved in neuronal pruning and migration, a process that is lacking in schizophrenia[33].

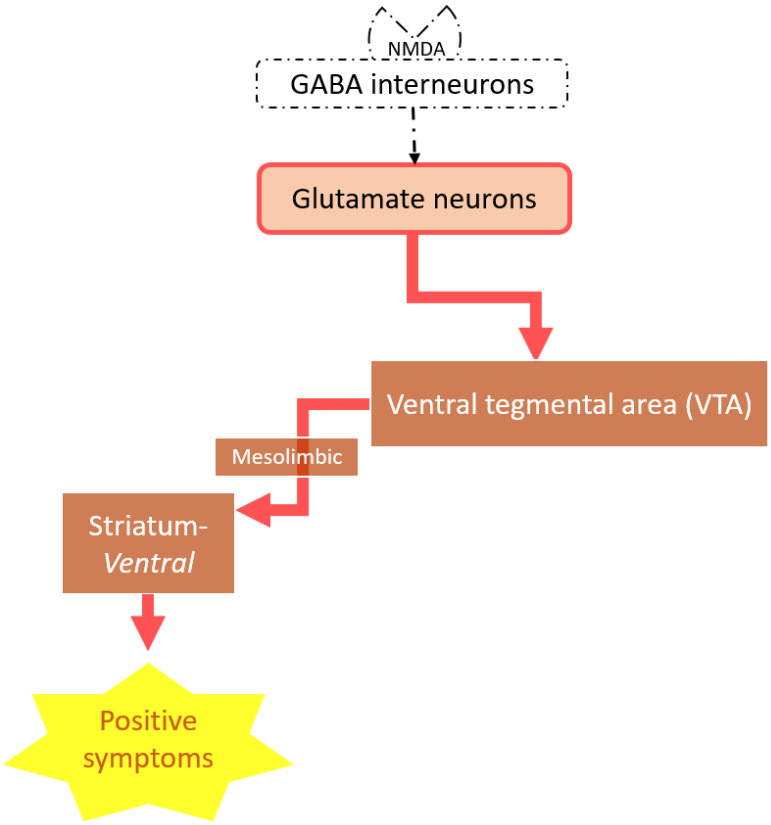

Figure 3. The glutamate link with dopamine pathways in schizophrenia. Adapted from Stahl et al. (2018)[32]

1.4. SYMPTOMS

Schizophrenia is a heterogeneous complex illness that is characterized by a wide variety of symptoms. According to the Diagnostic and Statistical Manual of Mental Disorder, 5th edition (i.e. DSM-5), the reference for diagnostic criteria of schizophrenia and other psychiatric illnesses, schizophrenia is characterized by at least two of the following symptoms: delusions,

hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms. In addition, some signs of the disorder must last at least 6 months (Table 1)[9].

Table 1. DSM-5 criteria for schizophrenia. Adapted from McCutcheon et al. (2020)[17]

DSM-5 criteria for schizophrenia
Criteria A, B and C must be fulfilled and other causes of symptoms excluded:
A) Two (or more) of the following symptoms must be present for a 1-month period or longer, and at least 1 of them must be item 1,2 or 3: 1. Delusions 2. Hallucinations 3. Disorganized speech (e.g. incoherence) 4. Grossly disorganized or catatonic behaviour 5. Negative symptoms (i.e. diminished emotional expression or avolition)
B) Impairment in level of functioning in one (or more) major areas, such as work, interpersonal relations, or self-care for a substantial period since the onset of the disturbance
C) Some signs of the disturbance must last for a continuous period of at least 6 months. This 6-month period must include at least 1 month of symptoms (or less, if treated), that meet criterion A (active-phase symptoms) and may include periods of residual symptoms. During residual periods, only negative symptoms may be present.

However, although these standardised criteria have provided consistency in the diagnosis of schizophrenia, allowing rapid and reliable identification of the illness with good sensitivity and specificity, they may not capture the whole picture[1], as they are not intended to be exhaustive. Although up to 11 dimensions of schizophrenic symptomatology have been described, the most commonly accepted characterisation is that symptoms can be classified into three main dimensions[34]. The first two are commonly accepted as positive

and negative symptoms, whereas the third dimension varies across definitions[3,17,35].

Positive symptoms, also known as psychotic symptoms, include hallucinations, delusions, excitement, hostility and suspiciousness[36]. A narrative review of the symptoms of schizophrenia described in the literature revealed that, among the positive symptoms, delusions were described by all authors and hallucinations by all but one, meaning that these are considered to be the hallmarks of the disorder[1]. Hallucinations are false perceptions, i.e. perception experiences occurring without an external stimulus[9], the most frequent being auditory hallucinations (e.g. hearing one's thoughts spoken aloud, hearing voices arguing or commenting[37]), except in children where visual hallucinations predominate[1,9]. Delusions are false beliefs, not understandable in term of cultural background[37], that are sustained despite undeniable conflicting evidence[9,38]. Delusions affect an average of 80% of people with schizophrenia[39]. Persecutory delusions, that is the belief that the individual will be hurt or harassed by someone else, a group of people or organisations, are the most frequent[9]. Other types of delusions are referential (i.e. belief that certain gestures, comments or environmental cues are directed at oneself), grandiose (i.e. belief in exceptional abilities), erotomanic (i.e. mistaken belief that another person is in love with oneself), nihilistic (i.e. conviction that a catastrophe is going to occur) and somatic (i.e. preoccupation regarding health or organ function)[9]. Delusions can be bizarre, when they are genuinely implausible[38]. Conversely, a non-bizarre delusion would be, for example, the belief that one is being watched by the police[9]. Positive symptoms, as they are more visible, are often the reason why people or their relatives seek medical help [17].

Negative symptoms are often the first symptoms to appear in schizophrenia, as they often occur during the prodromal state, even though they are not the primary cause of seeking care[23]. Negative symptoms represent a distinct dimension of the illness in all studies on the underlying symptom dimensions of schizophrenia [40]. Together with cognitive impairment, they are responsible

for the long-term disability associated with the illness[41], and poor outcomes[42]. Although not mandatory for the diagnosis of schizophrenia, up to 60% of patients experience these symptoms[23]. The most prominent negative symptoms are diminished emotional expression, also referred to as blunted affect, involving reduced facial or verbal expressivity, avolition (i.e. reduced self-initiated activity) and anhedonia (i.e. diminished ability to experience pleasure from positive stimuli). Decreased speech output (i.e. alogia) and asociality are also described, leading to five domains of negative symptoms[9,41,43] (Figure 4).

Figure 4. The negative symptoms of schizophrenia. Extracted from Correll C, & Schooler N (2020) [23]

It is important to distinguished between primary and secondary negative symptoms, especially in the assessment and treatment of persistent negative symptoms[41,43]. Primary negative symptoms are continuing symptoms, present regardless of the patient's medication[41], and considered to be intrinsically related to the pathophysiology of schizophrenia[23], whereas the secondary negative symptoms have an underlying cause[41], such as extrapyramidal symptoms, depressive symptoms, residual positive symptoms causing paranoid withdrawal, or sedative side effects.[41]

The third dimension of symptoms varies across studies and time, and there is still debate about whether schizophrenia is best characterised by a three- or five-dimensional model. Indeed, although a three-dimensional model is commonly used, five dimensions were found in a meta-analysis of exploratory factor analysis of the Positive and Negative Syndrome Scale (i.e. the PANSS)[35]. The PANSS is the most widely used scale for assessing symptoms of schizophrenia, but it is currently divided into three subscales[36]. Disorganisation is often mentioned as the third dimension of schizophrenia[3,34], and previous factor analysis found that the three dimensions disorganisation, positive and negative symptoms account for 65% of the total variance of the disorder[34]. However, disorganisation is included in the positive symptoms of schizophrenia in the PANSS[36], but it may also refer to cognitive impairment or to a separate entity. Indeed, in a recent factor analysis, conceptual disorganisation loaded with items reflecting different dimensions, such as stereotyped thinking (part of the negative symptoms of PANSS but no longer considered a negative symptom), poor volition (a commonly accepted negative symptoms) or low attention (cognitive impairment)[35].

Catatonic behaviour can also occur in schizophrenia, in up to 10% of patients[2], but although it has long been associated with schizophrenia, it is now considered a subtype of schizophrenia in the DSM-5, as it is also associated with other psychiatric disorders (e.g. bipolar disorder, major depressive disorder)[2,9]. Catatonia is characterised by decrease responsiveness to the environment, such as resistance to instructions,

maintenance of a rigid, inappropriate or bizarre posture, or lack of verbal or motor response (i.e. mutism and stupor). Conversely, patients may also be hyperkinetic, i.e. exhibit excessive and purposeless motor activity, which is also known as catatonic excitement. Finally, stereotyped movements, grimacing and echoing of speech are also described[2,9].

Cognitive impairment in schizophrenia was initially attributed to other symptoms or to psychotropic treatment. However, although one third of individuals remain neuropsychologically normal[44], it is established that cognitive deficits affect the majority of individuals with schizophrenia[9,44,45]. Evidence suggests that impairment in cognitive functions appears at or just before the onset of schizophrenia[44], but remains relatively stable thereafter[46], although cognition may worsen in the oldest patients[44,46]. The most severely affected neuropsychological function is attention, followed by declarative memory (i.e. memory of facts and events), processing speed, and executive functions (i.e. cognitive and behavioural responses to environmental demands allowing for control of action and long-term goal-directed behaviour)[45]. Cognitive symptoms, together with negative symptoms, are linked with poor functional and social outcomes[44].

Finally, although affective symptoms have sometimes been considered core symptoms of schizophrenia[34-36], some of these symptoms are now considered negative symptoms (e.g. anhedonia, blunted affect). Depressed mood may, however, occur during the course of the illness, but if a major mood episode is present for most of the total duration of the illness, the diagnostic of schizoaffective disorder should be made[9].

1.5. COURSE OF THE DISEASE

Schizophrenia is a chronic and fluctuating illness characterised after onset by different phases, such as the acute phase with severe positive and/or negative symptoms, the stabilisation phase when symptoms diminish, and the stable phase characterised by relative stable and mild symptoms, as

described in the US guidelines[47]. However, there is heterogeneity between patients in terms of disease progression[47]. Causes of relapse include stressful events, poor treatment adherence, and drug use (e.g. amphetamines, cannabis)[17] (Figure 5).

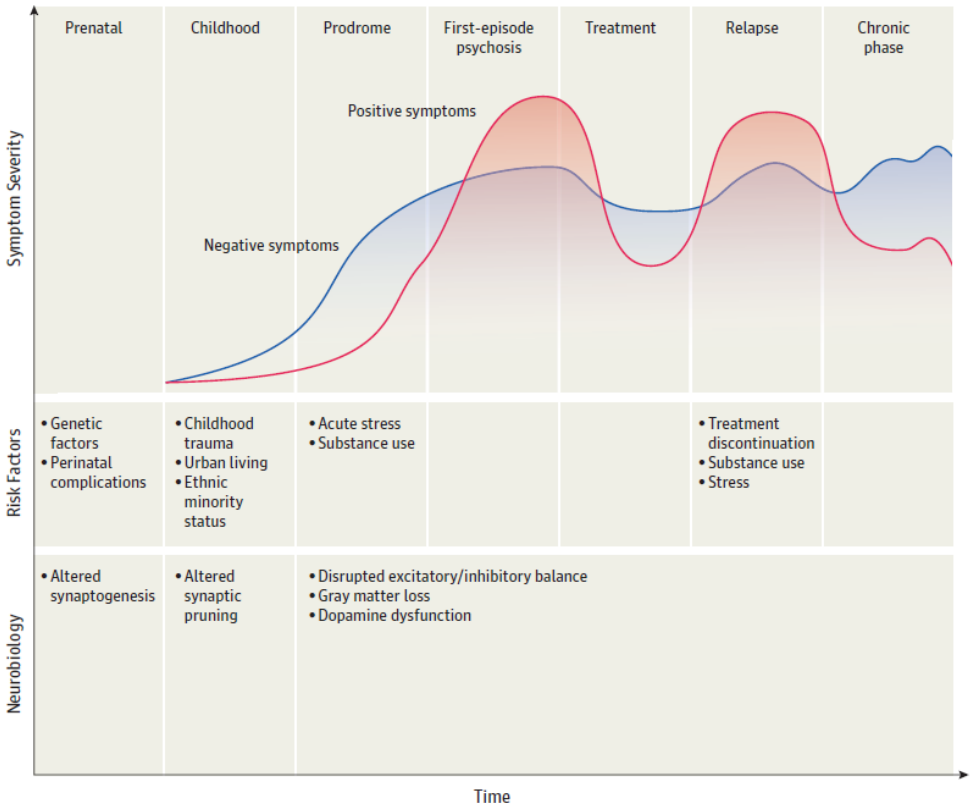

Figure 5. Clinical course of schizophrenia, risk factors and neurobiology of each phase. Extracted from McCutcheon R. et al (2020)[17].

The cycle of relapse and remission produces suboptimal and unsustained remission, ultimately leading to persistent cognitive and psychosocial impairement[47] (Figure 6). Patients with a premorbid better level of functioning, milder symptoms at baseline, an early response to antipsychotics and a shorter duration of untreated psychosis are more likely to be in

remission after a first episode of schizophrenia[48,49]. Persistence of negative symptoms is the main cause for non-remission[50].

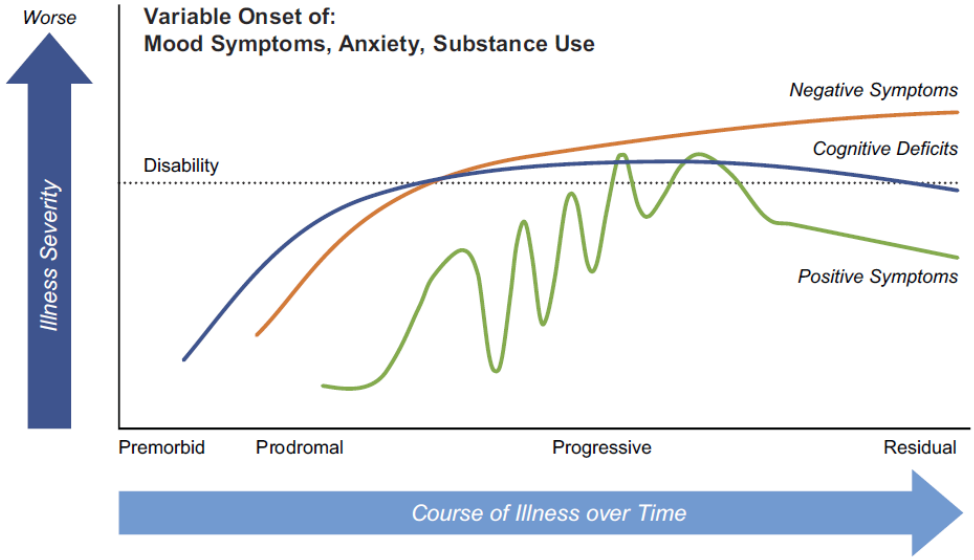

Figure 6. Changes in schizophrenia symptoms over time. Extracted from Correll C, Schooler N (2020) [23]

In addition to remission being based on symptoms, the severity and persistence of negative symptoms have been consistently linked to poorer functional outcomes in areas such as impaired occupational and academic performance, household integration, social functioning, participation in activities, and quality of life[23]. Therefore, to better emphasis on outcomes that matter to patients and their families, the concept of recovery has emerged, although there is no strict definition to date. Recovery is a long-term phenomenon that implies the ability to function well within the community, to be relatively free of disease symptoms, and to achieve relative autonomy. It is sometimes proposed that a GAF score ≥ 61 (out of 100) and improvement in both clinical and social areas, for at least 2 years define recovery[51]. Total recovery would be the return to pre-disease level of

functioning[51]. Functioning relates to activities of daily living (e.g. cooking, taking care of home)[51], social relationships, employment, and quality of life. Psychosocial interventions such a cognitive remediation, which ultimately lead to recovery, have been shown to work better on patients with fewer positive and negative symptoms, meaning that remission is necessary but not sufficient for recovery. In fact, cognitive deficit is a feature that limits the pace of psychosocial rehabilitation aimed at achieving recovery[44]. However, some patients may find coping solutions to function properly despite persistent illness[47]. Nevertheless, the median estimate of recovery for patients with schizophrenia is 13,5% (IQR 8.1%-20%)[51]. Poor recovery outcomes and reduced life expectancy are responsible for much of the burden of the disease. This is an important consideration in the treatment of schizophrenia, as we have moved from a focus on psychotic symptoms to a focus on recovery[44]. The potential worsening of cognitive symptoms by certain therapeutic choices, such as antipsychotic polypharmacy, is therefore of great importance, and the treatment of schizophrenia should be based not only relapse prevention, but also on long-term outcomes[47].

Finally, patients living with schizophrenia lose an average of 15 years of life, with a life expectancy around 65 years old[4,52]. This shorter life expectancy is due to a combination of factors. Firstly, people with schizophrenia develop more cardiovascular diseases and diabetes, due to a tendency towards an unhealthy lifestyle such as high sedentary way of life and poor diet.[52] Secondly, individuals with schizophrenia have a higher prevalence of alcohol misuse, tabaco smoking and substance abuse. Thirdly, they tend to make less use of healthcare, which delays the diagnosis of potentially life-threatening diseases. High polygenic risk scores for schizophrenia have also been recently associated with certain cardiac phenotypes, such as reduced cardiac volume, increased ejection fractions, and increased myocardial stiffness and diastolic dysfunction. This phenotype may further worsen cardiac outcomes of patients with schizophrenia[53]. Their risk of suicide is also greatly increased, accounting for 5% of mortality in these patients[3].

1.6. TREATMENT: ANTIPSYCHOTICS AND OTHER TREATMENT OPTIONS

TREATMENT RESPONSE AND OUTCOMES

Three scales are regularly used in most studies of schizophrenia: the Brief Psychiatric Rating Scale (i.e. BPRS), the PANSS, already mentioned, and the Clinical Global Impression scale (i.e. CGI).

The BPRS[54] was developed in 1962 to provide an effective, rapid and reliable evaluation of psychiatric patients change. It contains 16 symptom areas that were selected on the basis of factor analyses of larger scales and on discrete symptom domains identified in previous research (Table 2). The scale provides a brief description of each area. The severity of each symptom is rated on a 7-point unipolar scale (Table 3). The reliability of the scale was first validated in 83 newly admitted schizophrenic patients[54], but intra- and inter-rater reliability was confirmed by further analyses from other research groups[55].

The PANSS was developed in 1987 and aimed to standardise measures of the different dimensions of schizophrenia in order to obtain an operational and medication sensitive tool. The development of the PANSS items was inspired by the BPRS and the Psychopathology rating schedule, and includes positive symptoms, negative symptoms, and global psychopathology. The positive and negative symptoms chosen are those that have been unambiguously and consensually defined as primary symptoms for positive symptoms, and considered primary rather than secondary for negative symptoms, as explained in the previous section. The PANSS contains 30 items (Table 2), for which the severity of symptoms is rated from 1 (i.e. absent) to 7 (i.e. extreme) (Table 3), leading to a total score between 30 and 210. A brief description of the meaning of the severity of each symptom is also provided. For example, mild delusions (i.e. score 3) are described as follows: "Presence of one or two delusions that are vague, uncrystallized, and not tenaciously held. Delusions do not interfere with thinking, social relations, or behaviour"[36]. The PANSS was first developed and validated in a sample of 101 schizophrenic patients[36],

but its strong psychometric characteristics have been demonstrated repeatedly since then[56].

Both scores were originally developed for research purposes[54], but they are time-consuming[57], and require experience in using the scale, without which reliability can be reduced[54]. These factors limit their possible use in real practice. For these reasons, the Clinical Global Impression scale (i.e. CGI) was developed for use in NIMH-sponsored trials (i.e. National Institute of Mental Health of the United States), with the aim of developing a scale that is easily understood and quick to operate (1 to 2 minutes) for non-researcher clinicians. There are two subtypes of CGI: the CGI-Severity (CGI-S) and the CGI-Improvement (CGI-I). The CGI-S consists of an item that assesses the severity the psychopathology and symptoms observed over the past 7 days, with a score ranging from 1 ("normal") to 7 ("among the most severely ill patients") (Table 3), by asking the following question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" (Table 2). Raters must be clinicians who are familiar with the disease (i.e. any mental illness). The CGI-I is intended to measure the change in the patient's psychopathology from the situation prior to the initiation of the medication (i.e. baseline). The CGI has been shown to be as sensitive as the BPRS in detecting differences in efficacy between antipsychotics[58], and as it is shorter and simpler, this scale is useful in naturalistic clinical trial where longer scales would affect the normal course of care[59].

Table 2. The PANSS, the BPRS and the CGI scales

PANSS	BPRS	CGI
Positive scale Delusions Conceptual disorganization Hallucinatory behaviour Excitement Grandiosity Suspiciousness Hostility **Negative scale** Blunted affect Emotional withdrawal Poor rapport Passive-apathetic social withdrawal Difficulty in abstract thinking Lack of spontaneity & flow of conversation Stereotyped thinking **General Psychopathology Scale** Somatic concern Anxiety Guilt feelings Tension Mannerisms & posturing Depression Motor retardation Uncooperativeness Unusual thought content Disorientation Poor attention Lack of judgment & insight Disturbance of volition Poor impulse control Preoccupation Active social avoidance	Somatic concern Anxiety Emotional withdrawal Conceptual disorganization Guilt feelings Tension Mannerisms & posturing Grandiosity Depressive mood Hostility Suspiciousness Hallucinatory behaviour Motor retardation Uncooperativeness Unusual thought content Blunted affect	**CGI-Severity (CGI-S)** Considering your total clinical experience with this particular population, how mentally ill is the patient at this time? **CGI-Improvement (CGI-I)** Compared to the patient's condition at admission to the project [prior to medication initiation], this patient's condition is:

Table 3. Rating for severity of each symptoms area in the PANSS, BPRS and CGI scales

PANSS	BPRS	CGI
1. Absent. 2. Minimal. 3. Mild. 4. Moderate. 5. Moderate severe. 6. Severe. 7. Extreme.	1. Not present. 2. Very mild. 3. Mild. 4. Moderate. 5. Moderate severe. 6. Severe. 7. Extremely severe.	**CGI-S** 1. Normal, not at all ill 2. Borderline mentally ill 3. Mildly ill 4. Moderately ill 5. Markedly ill 6. Severely ill 7. Among the most extremely ill patients **CGI-I** 1. Very much improved since the initiation of treatment 2. Much improved 3. Minimally improved 4. No change from baseline (the initiation of treatment) 5. Minimally worse 6. Much worse 7. Very much worse since the initiation of treatment

In addition to being time-consuming and requiring specific training, the clinical significance of PANSS or BPRS total scores may not be clear. Some studies have therefore attempted to link their scores with the CGI, which is considered more clinically meaningful, in order to translate research findings into clinical practice[56,60]. A very good correlation between the CGI, PANSS and BPRS has been found, allowing equivalence between scores, as described in table 4. For example, disease severity, a CGI score of 5, indicating "markedly ill", would correspond to a BPRS score of 52-55 and a PANSS of 93-96, and a CGI of 7, i.e. "among the most extremely ill patients" would correspond to a BPRS score of 83-89 and a PANSS of 143-149, based on both clinical trials and replication in a naturalistic sample[56,60,61]. Regarding the response to treatment, slightly different equivalences were found, depending on the week following the initiation of the treatment[56], and some correlations are

expressed as absolute change in score while others are based on relative reduction[56,60,61]. Still, the correlation between the scales remains very good (Figure 7)[56,58,61]. It is commonly accepted that a 20-25% reduction in the PANSS corresponds to a 1-point improvement in the CGI, and a 40-50% reduction to a 2-point improvement on the CGI[42]. However, in most clinical trials, the minimum response is defined by a 20% reduction in the PANSS and BPRS rather than 25% and a 1-point improvement in the CGI for an acute psychotic episode[42].

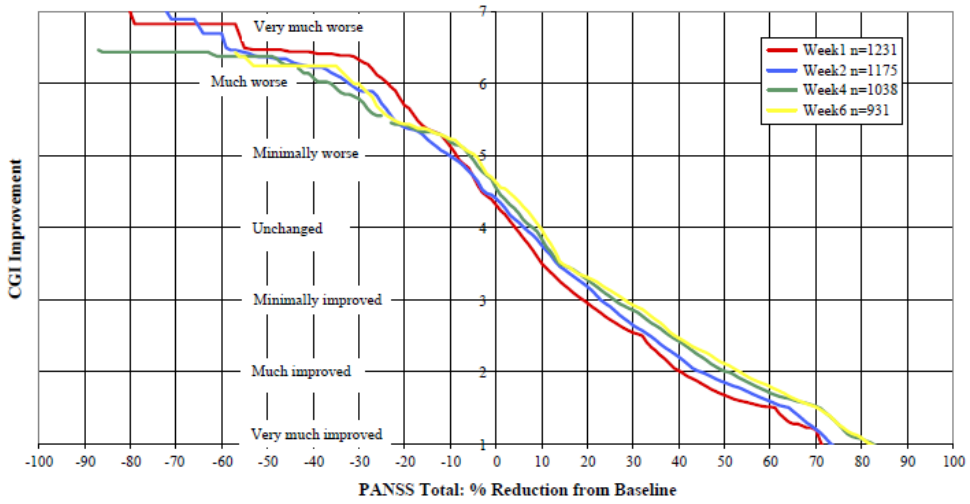

Figure 7. Correlation between the percentage of PANSS reduction from baseline and the CGI-Improvement score. Extracted from Leucht S. et al (2005)[56].

Table 4. Comparison between the PANSS, the BPRS and the CGI-S

	PANSS	BPRS	CGI-S
Time to complete	30-40 minutes	20 minutes	1-2 minutes
Range of score	30 to 210	18 to 126	1 to 7
Interpretation and linking between scales (total score)	57-61	30-36	3. Mildly ill
	73-78	40-45	4. Moderately ill
	93-96	52-55	5. Markedly ill
	115-118	64-70	6. Severely ill
	143-149	83-89	7. Among the most extremely ill patients

Another dimension to consider is the time required to assess response or lack of response to the treatment. Although current guidelines still recommend a 6-weeks period to assess treatment response[42,62], most of the response to antipsychotics occurs within the first 3 weeks after introduction (i.e. early response). In fact, many studies have demonstrated that symptom reduction is greater during the first 2 to 4 weeks than during the rest of the year[63,64] and lack of response at week 2 (i.e. less than 20% of reduction on the PANSS or BPRS scales, or a score of 4 or more on the CGI-I scale) correctly identifies non-responders in up to 87% of cases[65-67].

Last but not least, and although not used in most RCT because it was not intended to be, the American Psychiatric Association developed the Global Assessment of Functioning scale (GAF), which was first published in the 3rd revised edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) in 1987[68]. The aim was to address the need for rapid indicators in the provision of mental health services. The GAF measures the overall psychopathological disturbance of a patient with a mental illness, with the aim of encompassing symptomatology and social functioning, and has proven to be satisfactory reliable[69]. For that reason, every patient admitted to a psychiatric unit in Belgium must have a GAF score given by a psychiatrist, both

on admission and at discharge[70]. The GAF score ranges from 0 (i.e. worse functioning) to 100 (i.e. no symptoms and good functioning in all area). The scoring consists of 9 descriptors ranging from 1 to 9, each descriptor having a nine-point range (Table 5)[69]. However, it has been shown that the GAF is not very concordant with the PANSS and CGI, possibly due to the complexity of the factors to consider for the rating[71]. This is particularly true when raters are untrained or have a negative attitude toward GAF and measurement instruments in the field of psychiatry in general[72]. Furthermore, GAF scores seem to have minimal correlation with treatment outcomes, despite most of the assessment is based on symptoms rather than functioning[73], and reliability seems to be quite low at the individual level compared to the group level[72]. For these reasons, the DSM-5 no longer uses the GAF score for assessing patient functioning[9].

In addition to the scales used in most RCT of antipsychotics or in clinical routine, the development of pharmacoepidemiology has led to the use of other factors as indicators of treatment response. Indeed, the rate of psychiatric rehospitalisation after hospital discharge[74], risk of all-cause hospitalisation or unplanned admission[75] enable to detect health care utilisation.

Table 5. Global Assessment of Functioning (GAF) scale[69]

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment in functioning due to physical (or environmental) limitations.

Code	Note: Use intermediate code when appropriate
100-91	**Superior functioning** in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms.
90-81	**Absent or minimal symptoms** (e.g., mild anxiety before an exam), good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns (e.g., occasional argument with family members).
80-71	**If symptoms are present, they are transient and expectable reactions to psychosocial stressors** (e.g., difficulty concentrating after family argument), no more than slight impairment in social, occupational or school functioning (e.g. temporary falling behind in schoolwork).
70-61	**Some mild symptoms** (e.g., depressed mood and mild insomnia) **OR some difficulty in social, occupational, or school functioning** (e.g. occasional truancy, or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationship.
60-51	**Moderate symptoms** (e.g., flat affect and circumstantial speech, occasional panic attacks) **OR moderate difficulty in social, occupational, or school functioning** (e.g., few friends, conflict with peers or co-workers).
50-41	**Serious symptoms** (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) OR any serious impairment in social, occupational, or school functioning (e.g., no friends, unstable to keep a job).
40-31	**Some impairment in reality testing or communication** (e.g., speech is at times illogical, obscure, or irrelevant) **OR major impairment in several areas**, such as work or school, family relations, judgment, thinking or mood (e.g., depressed man avoids friends, neglects family, and is unable to work, child frequently beats up younger children, is defiant at home, and is failing at school).
30-21	**Behaviour is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment** (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation), OR inability to function in almost all areas (e.g., stays in bed all day, no job, home, or friends).
20-11	**Some danger of hurting self or others** (e.g., suicide attempts without clear expectation of death, frequently violent, manic excitement) **OR occasionally fails to maintain minimal personal hygiene** (e.g., smears faeces) **OR gross impairment in communication** (e.g., largely incoherent or mute).
11-1	**Persistent danger of severely hurting self or others** (e.g., recurrent violence) **OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death.**
0	Inadequate information.

Finally, although response to antipsychotics is often defined as a 20% reduction in the PANSS and BPRS scales, or a 1-point improvement in the CGI scale, this does not adequately reflect the patient's absolute, long-term state. Consequently, a consensus definition of remission has been proposed based on an absolute threshold of symptom severity. The remission criterion is met when a patient obtains a score of 3 or less on the PANSS or BPRS scales for eight main symptoms: delusions, conceptual disorganisation, hallucinatory behaviour, unusual thought content, mannerism and posturing, blunted affect, passive/apathetic social withdrawal, and lack of spontaneity and flow of conversation. This state must last for at least six months, also individuals may experience some fluctuation in symptoms, but without any major change in their functioning or well-being. This score would correspond to mild symptoms or no symptoms at all[47]. However, remission is difficult to define for psychosocial and cognitive functioning because there is not enough studies looking at the correlation between symptom reduction and cognition and global function[47].

PHARMACOLOGY OF ANTIPSYCHOTICS- EFFICACY

Antipsychotics are the only drugs registered to date for the treatment of schizophrenia. The pharmacology underlying their efficacy is described below, with an emphasis on the most commonly accepted mode of action.

- Dopamine D_2 receptors

Antipsychotics have been used for a decade since the discovery of chlorpromazine without knowledge of their mode of action, but studies in the early 1960s using imaging techniques demonstrated that they all acted by blocking dopamine D_2 receptors, with the aim of reducing overactive dopamine pathways[76,77]. Moreover, other in vivo PET studies using radiolabelled antipsychotics have shown a linear relationship between the percentage of D_2 receptor occupancy and the reduction of psychotic symptoms[78,79] and that at least 60-65% of D_2 receptors need to be blocked

by full antagonists to achieve the desired efficacy[77,79,80]. On the other hand, it was also found that an occupancy of more than 80% of these receptors increased the risk of extrapyramidal symptoms[78,79]. In addition, a minimum daily dose threshold was found for relapse prevention in the maintenance treatment of patient with stable schizophrenia[81]. Based on these results, a therapeutic window of 65% to 80% of the D_2 receptors occupancy has been proposed[42,77,82] (Figure 8). This would correspond, for example, to 2-4mg risperidone or 10-20 mg olanzapine[77]. However, this occupancy is better predicted by plasma concentrations of these drugs rather than by their dosage[82], and Ki, the concentration of drug required to block half of the receptors, is used to compare the affinity of different drugs for different receptors[76]. An exception to this blocking range rule is for partial agonist, such as aripiprazole, for which a minimum of 80-85% occupancy is required to obtain a clinical response[76,83].

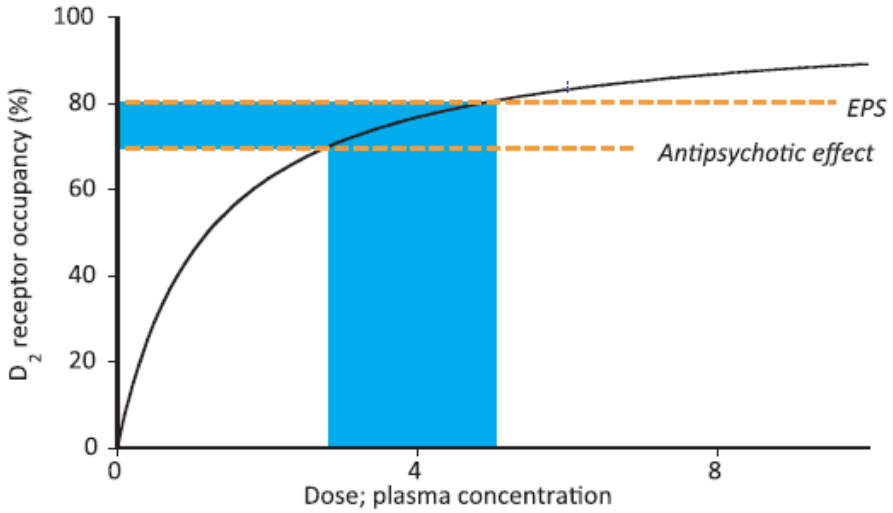

Figure 8. Therapeutic window of antipsychotic drugs based on the relationship between their plasma concentration and D_2 receptors occupancy. Extracted from Nord M & Farde L (2001)[77]. Abscise axis represents doses or plasma concentrations which are arbitrary values for illustration.

Given this consideration, it is expected that all antipsychotics have similar efficacy, since they act in the same way. This pharmacological assumption is confirmed both by meta-analysis of RCTs[84] and by cohort studies in real clinical practice, with the exception of clozapine[74]. Antipsychotics are highly effective compared to placebo, with a number needed to treat (NNT) of 3 for relapse prevention[85] and between 2 and 5 for symptom reduction (i.e. 40% reduction in BPRS or "much improved" in CGI)[86].

- Serotonin 5-HT_{2A}

The ability of antipsychotics to block D_2 receptors is a predictor of their efficacy. However, the observation that psychedelic drugs, such as lysergic acid diethylamide (LSD) and psilocybin, which are 5-HT_{2A} agonists, induced visual hallucinations and delusions, led to the hypothesis that serotonin is involved in the pathophysiology of psychosis[32]. The development of 5-HT_{2A} receptor antagonists was therefore hoped to effectively treat the symptoms of schizophrenia. As a consequence, second-generation antipsychotics (SGA) that antagonise these 5-HT_{2A} receptors, in addition to the dopamine D_2 receptors, were introduced[87]. Unfortunately, no clinically significant differences have been identified between the first and the second generation of antipsychotics in terms of efficacy regarding positive symptoms[84]. It should be noted that the categorisation between first- and second-generation antipsychotics is not only based on the ability to antagonise the 5-HT_{2A} receptors, but also on their side effect profiles, which will be detailed below.

Nevertheless, although serotonin is certainly involved in psychosis, the $5HT_{2A}$ inverse agonist pimavanserin, with no antidopaminergic activity, is effective in Parkinson disease's psychosis[88], although controversial[89] and not approved by the European Medicines Agency, but shows no significant benefit on PANSS or CGI scores in schizophrenia[89], confirming a different pathophysiology between these two psychoses. Indeed, the psychosis of Parkinson's disease is thought to be due to excessive activation of the 5-HT_{2A} receptors[32].

In addition to psychotic symptoms, blocking 5-HT_{2A} receptors in the mesocortical pathway is thought to increase the dopamine release in the

prefrontal cortex, thereby reducing, or at least not worsening, the negative and cognitive symptoms of schizophrenia[90]. However, only four SGA (i.e. olanzapine, clozapine, risperidone and sertindole) were found to be more effective than first-generation antipsychotics (FGA) in reducing the negative symptoms[91], even though they all target the 5-HT_{2A} receptors. Furthermore, the demonstration of improvement in negative symptoms by these 4 antipsychotics was based on clinical trials where the response to treatment was primarily focused on positive symptoms, and it cannot be excluded that the improvement in negative symptoms is due to the reduction in social withdrawal generated by delusions, improvement in depressive symptoms and extrapyramidal side effects, the so-called secondary negative symptoms[23,84]. Moreover, amisulpride, the only antipsychotic registered in Europe for the treatment of negative symptoms prior to third generation cariprazine, which will be detailed later, was found to reduce negative symptoms only against placebo, but a parallel reduction in depressive symptoms was observed, again not ruling out the hypothesis of a reduction in secondary negative symptoms[23]. Indeed, SGA were found to be more effective in improving social functioning[84] and quality of life[92]. Finally, a recent study of pimavanserin (i.e. the $5HT_{2A}$ partial agonist without dopaminergic activity) showed that it slightly reduced negative symptoms of schizophrenia, although the trial was against placebo[93]. In conclusion, the reduction of negative symptoms is no longer considered a core characteristic of the SGA[91].

- Glutamate NMDA receptors

Clozapine, as mentioned above, is more effective than other antipsychotics[84], including in patients with treatment-resistant schizophrenia (i.e. without significant improvement in symptoms after 2 adequate trials of antipsychotics in terms of dosage and duration)[94]. This difference may be explained by its different pharmacological profile from that of the above-mentioned antipsychotics. Indeed, it only needs to block on average 40-50% of D_2 receptors to be effective[95,96]. It was initially suspected that it exerted its superior efficacy through the blockage of the serotonin 5-HT_{2A} receptors[96]. However, all atypical antipsychotics are also antagonists of these receptors

without reaching the same level of efficacy[90]. The findings that NMDA receptors were enhanced in rodent treated with clozapine[97], and that clozapine displaced NMDA receptor ligands in rat striatum, suggest that clozapine also targets the glutamate NMDA receptors, perhaps through partial agonism[33], which may explain its unique efficacy profile. This hypothesis is further strengthened by the recent contribution of genetics that has led to the most commonly accepted dopamine/glutamate hypothesis for schizophrenia.

- Dopamine D3 receptors

Interestingly, although pathophysiology has long focus on D_2 receptors, D_3 receptors are increasingly being studied, particularly their involvement in negative symptoms. The main hypothesis is that antagonism of D_3 receptors enhances dopaminergic transmission in the prefrontal cortex and nucleus accumbens. Hypodopaminergic transmission in these two areas has been linked to the negative symptoms of schizophrenia[23]. The partial agonism of cariprazine at D3 receptors could explain its efficacy against the negative symptoms of schizophrenia[98]. In fact, cariprazine is the only antipsychotic to have demonstrated a statistically significant greater reduction in negative symptoms than risperidone, in patients not suffering from depression or extrapyramidal symptoms. The reduction in positive symptoms was not significantly different between the two drugs, which rules out its efficacy only on secondary negative symptoms. However, the difference in least squares mean change in PANSS factor score for negative symptoms (PANSS-FSNS) between the 2 drugs at week 26 was only 1.46 (–8.90 points for cariprazine versus –7.44 points for risperidone, p=0.0022). This difference suggests a non-clinically meaningful difference. Finally, cariprazine improved functioning to a greater extent than risperidone (14.30 points for cariprazine versus 9.66 for risperidone, p<0.0001), leading the authors to suggest that this was clinically significant for patients. Further studies, not sponsored by the marketing authorisation holder, are needed to better understand the added value of cariprazine, as well as the involvement of D3 receptors in negative symptoms.[99].

PHARMACOLOGY OF ANTIPSYCHOTICS- SIDE EFFECTS

Antipsychotics are generally classified not only according to whether they antagonise 5-HT_{2A} receptors, but also according to their side-effect profile. However, this categorisation is fairly arbitrary and is regularly rechallenged, as some FGA have adverse effects similar to those of the SGA (e.g. weight gain induced by chlorpromazine), while some SGA have adverse effects similar to those of the FGA (e.g. extrapyramidal symptoms induced by risperidone).

- Extrapyramidal symptoms

All current antipsychotics are D_2 receptor blockers, not only in the mesolimbic pathway, but also in the nigrostriatal, mesocortical and tuberoinfundibular pathways.

Blockade of D_2 receptors in the dorsal striatum (i.e. the nigrostriatal pathway) induces what are known as extrapyramidal symptoms (EPS), which are classified into four subtypes: drug-induced parkinsonism, acute dystonia, akathisia, and tardive dyskinesia. Parkinsonism includes tremor, rigidity, bradykinesia (i.e. slowed movement) and masked face[100] and can be difficult to differentiate from Parkinson's disease (Table 6). It should be noted that, although D2 receptor blockade occurs within hours after taking the antipsychotic, parkinsonism develops within months of taking the drug, with half to ¾ of people developing parkinsonism within a month of starting, and 90% within 3 months[100]. Acute dystonia is characterised by involuntary, intermittent or sustained muscle contractions, especially in the face, neck, extremities and even eyes, while akathisia is a feeling of inner restlessness[101]. Finally, tardive dyskinesia is a syndrome of late-onset involuntary abnormal movements, with an annual incidence of 5%. This hyperkinetic movement disorder is induced by the time-dependant upregulation of D_2 receptors[101] following chronic blockade. FGA induces the highest risk, particularly in the elderly[102]. Parkinsonism and dystonia are also more common with FGAs, as these drugs do not block the serotonin 5-HT_{2A} receptors[101,103]. Conversely,

SGAs block the serotonin 5-HT_{2A} receptors with higher affinity than D2 receptors, which would increase dopamine release in the striatum, displacing D_2 blockers from D_2 receptors and restoring dopamine transmission, leading to a reduction in EPS[90]. This hypothesis is somewhat controversial, firstly because risperidone induces the same incidence of EPS as amisulpride, which has no affinity for 5-HT_{2A}[104], and secondly because the reduction in EPS risk was associated with affinity for 5-HT_{2C} and not 5-HT_{2A} in a meta-regression analysis[105]. However, one explanation is that if the affinity for the D_2 receptors becomes similar to that of the 5-HT_{2A} receptors, which occurred at higher doses of risperidone and paliperidone[90], dose-dependent EPS appears, albeit to a lesser extent than FGA, which is confirmed by the frequency of use of antiparkinsonian medications[84]. Furthermore, the hypothesis that 5-HT_{2C} receptors are linked to EPS is mainly based on the fact that olanzapine, clozapine and quetiapine are the SGAs with the least EPS, and that they have a high affinity for $5HT_{2C}$ receptors[84,106], although this may also be due to their affinity for 5-HT_{1A} receptors. Partial agonism of 5-HT_{1A} receptors are in fact also commonly cited as being involved in the prevention of motor adverse effects[76,101].

Finally, blocking M_1 receptors is also linked to protection against EPS[105], and M_1 blockers, known in psychiatry as anticholinergics or antiparkinsonian drugs, are the reference treatment for EPS (Table 6)[107]. This is because there is a reciprocal balance between acetylcholine and dopamine in the striatum, where stimulation of the dopamine receptors located in the nigrostriatal cholinergic interneurons leads to an increase in the release of acetylcholine, which stimulates the GABAergic neurons, thereby inhibiting movement. By blocking M_1 receptors, drugs with anticholinergic properties prevent this stimulation of GABA neurons, thereby protecting against motor adverse effects[101]. This effect could also explain the lower propensity of olanzapine, clozapine and quetiapine to induce EPS, as they have a high affinity for M_1 receptors[76] (Figure 9).

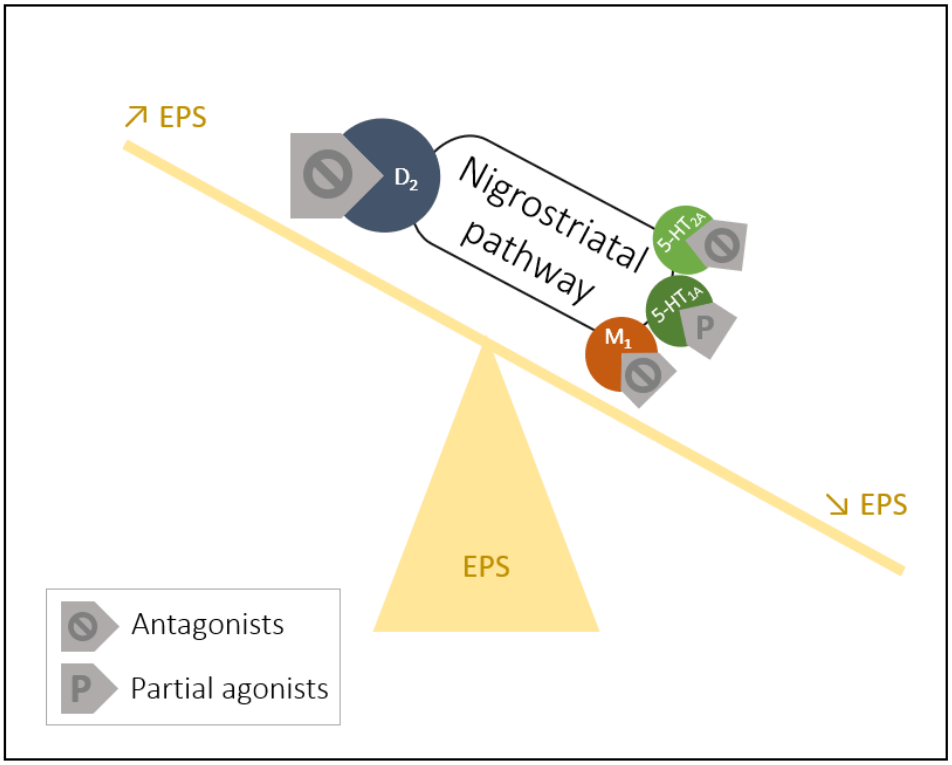

Figure 9. Impact of receptors antagonism or partial agonism in the nigrostriatal pathway on extrapyramidal symptoms.

Antagonism or partial agonism of D_2 receptors increases the risk of extrapyramidal symptoms, while antagonism of 5-HT_{2A} and M_1 receptors and partial agonism of 5-HT_{1A} receptors reduce the risk of extrapyramidal symptoms. EPS: Extrapyramidal symptoms

- Prolactin increase

D_2 receptors and 5-HT_{2A} receptors are also found in the lactotroph cells of the pituitary gland, where they regulate prolactin secretion. Dopamine inhibits the secretion of prolactin while serotonin stimulates it. Antipsychotics that block more D_2 receptors than 5-HT_{2A} receptors therefore induce hyperprolactinemia (i.e. prolactin levels above 20 ng/mL in men and 25 ng/mL in women) in a dose-dependent manner, whereas SGAs with a higher affinity for 5-HT_{2A} receptors than D_2 receptors have a lower risk of causing

side effects (Table 6)[101]. Hyperprolactinemia induces sexual dysfunction, anovulation, gynecomastia and sometimes galactorrhea[107], and occurs in 13 to 40% of patients taking antipsychotics[104,108]. Several studies have also linked hyperprolactinemia to reduced bone mineral density and hip fracture[107]. Concerns have also been expressed about the potential increased risk of breast cancer in patients with high prolactin levels, but the results are inconsistent and reassuring[107,109]. It should be noted that partial agonism on D_2 receptors maintains the inhibition of secretion, which explains why aripiprazole can sometimes be used at low doses to reduce prolactin levels[104,110]. Finally, clozapine presents a low risk due to its low occupancy of D_2 receptors[104].

- Weight gain and metabolic syndrome: H_1 and 5-HT_{2C}

A well-known side effect of antipsychotics is weight gain, with, consequently, an increased risk of metabolic syndrome, including diabetes. Although this effect is often considered to be an essential feature of SGAs, FGAs also present, to a lesser extent, a risk of weight gain [84,104,111]. Various mechanisms are involved. Firstly, D_2 receptor blockade is associated with disruption of the reward signal (i.e. conditioned learning) associated with food intake and satiety[104]. Secondly, blockade of the serotonin 5-HT_{2C} receptors induces hyperphagia[111,112], and polymorphism of these receptors has been implicated in eating disorders, such as anorexia. Finally, it seems that the main mechanism of weight gain induced by antipsychotics is through antagonism of H_1 receptors, which are known to increase appetite and therefore food intake, leading to obesity[112] (Figure 10). These results are consistent with the meta-regression analysis which showed that H_1 and 5-HT_{2C} receptors were associated with weight gain[105]. In conclusion, antipsychotics with antagonism of both H_1 and 5-HT_{2C} receptors have the highest risk of inducing weight gain (e.g. clozapine, olanzapine)[76,84], followed by those acting only on H_1 receptors, and then pure D_2 blockers (e.g. amisulpride)(Table 6) [111].

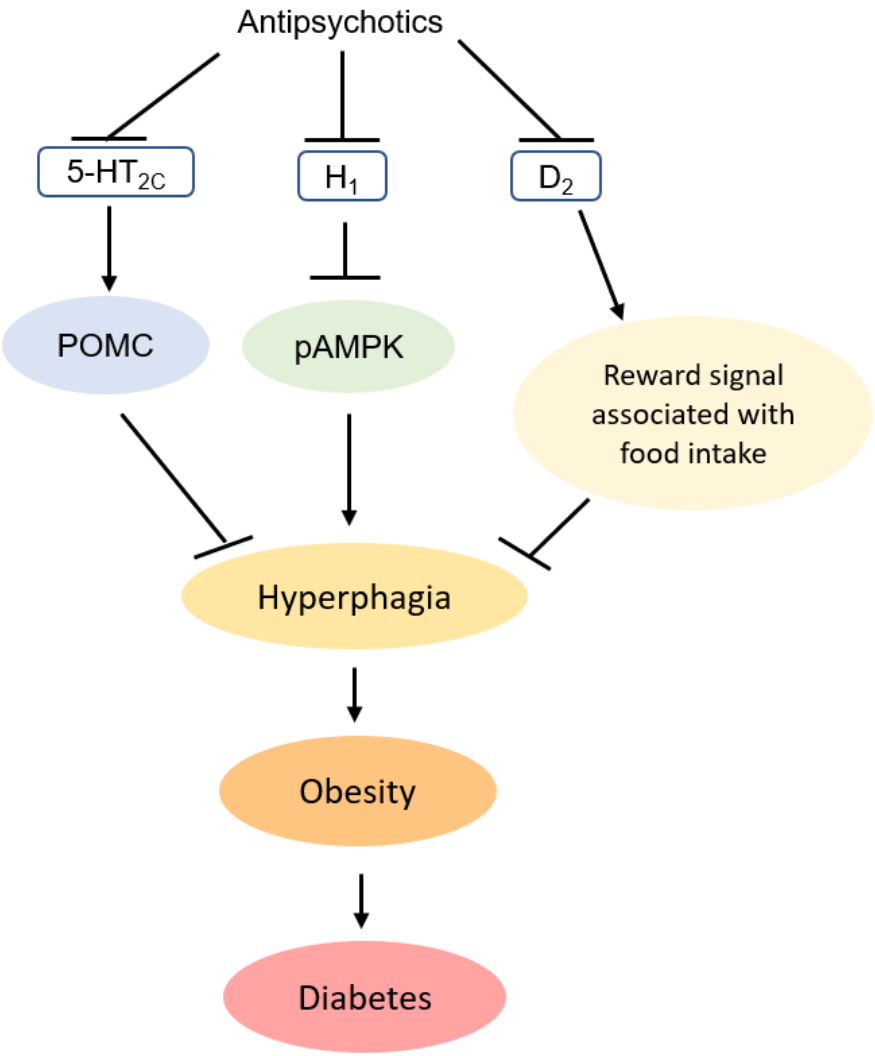

Figure 10. Mechanism of antipsychotics induced weight gain and diabetes. Adapted from Chen J. et al (2017)[112]

pAMPK: Phosphorylated -AMP-activated protein kinase; D2: Dopamine D2 receptors; 5-HT2C: Serotonin 5-HT2C receptors; H1: Histamine H1 receptors POMC: proopiomelanocortin

Patients with schizophrenia are more than twice as likely to develop type 2 diabetes[113]. Although the increased risk of metabolic disease is due not only

to antipsychotics, but also to sedentarily and life style (e.g. smoking, alcohol misuse), it is important to monitor weight on a daily basis and to avoid prescribing antipsychotics that have the greatest potential for weight gain as a first-line treatment[114].

- Anticholinergic side effects

As mentioned above, some antipsychotics are M_1 muscarinic receptor antagonists, which, notwithstanding their protective effect against EPS, induce anticholinergic side effects such as dry mouth, blurred vision, urinary retention and constipation[104,107]. Central blockade of M_1 receptors can also cause memory loss and cognitive impairment, which can worsen cognitive symptoms (Table 6)[104].

- Sedation

In addition to increasing appetite, H_1 receptor antagonism induces sedation, which explains the sedative properties of clozapine, quetiapine and olanzapine, as well as all the low-dose antipsychotics that are used in the treatment of insomnia[104]. Dizziness, fatigue, postural hypotension and sedation are also induced by antagonism of postsynaptic norepinephrine α1 receptors (Table 6)[76,115] . Antipsychotics combining H_1 and α1 receptor antagonism are therefore expected to be even more sedating (e.g. clozapine, quetiapine, clotiapine, prothipendyl).

- QTc prolongation

Antipsychotics are associated with a 3-fold increased risk of sudden cardiac death[116], but the risk depends upon the drug used and other risk factors, with sertindole exhibiting the highest risk[84]. Various causes have been suggested, but ventricular tachycardia and torsades de pointe appear to be the most common cause of sudden cardiac death in patients taking antipsychotics. Prolonged QTc interval (>440 ms for men and >470 ms for women) has proved to be a good indicator for monitoring this risk, although it is not perfect. In fact, certain drugs such as amiodarone often prolong the QTc interval but rarely cause torsades de pointe, whereas quinidine more often

causes torsades de pointe although it more rarely causes severe QTc prolongation[117].

Nevertheless, despite these limitations, it is the best predictor for torsade de pointe available to date, particularly those induced by antipsychotics. Indeed, while tricyclic antidepressants prolonged the QTc interval by blocking the sodium channels, thus inducing arrythmia only in patients with pre-existing cardiac diseases (e.g. bundle branch block) or in case of overdose, antipsychotics induce QTc prolongation by blocking the hERG (human ether-a-go-go-related gene) potassium channels (Table 6)[117,118]. These channels are responsible for the rapid delayed rectifier K^+ currents of the phase 3 repolarisation phases of the ventricular myocytes[119]. Blockade of these channels results in delayed myocyte repolarisation, which prolongs the QTc interval and ultimately leads to torsade de pointe and complete heart block[119]. Prolongation of QTc interval is dose-dependent (except with ziprasidone), and the risk is higher in women, in people with congenital long QTc and in cases of K^+ depletion. A QTc interval greater than 500 ms is often considered to be the threshold for a high risk of torsades de pointe[117].

It is important to note that, although antipsychotics have long been suspected of increasing mortality, this does not appear to be the case, perhaps partly due to a reduction in suicidal deaths[120], but not only[121]. In fact, antipsychotic use has even been shown to reduce the risk of death in schizophrenia compared to no use, and long-term use further reduces this risk[121]. However, monitoring of ECG and plasma potassium concentration, as well as screening for risk factors (e.g. alcohol use disorder, malnutrition, family history suggestive of long QT syndrome) is recommended in clinical routine[42].

Table 6. Effects of antipsychotics related to their pharmacologic profile.
Adapted from Mauri MC. Et al (2014)[106]

Mechanism	Effects on schizophrenia symptoms	Effects on adverse events
D_2 antagonism	↘ positive symptoms	↗ EPS ↗ Prolactinemia Disrupt reward signal associated with food intake and satiety
D_2 partial agonism	↘ positive symptoms	Akathisia = or ↘ prolactinemia (add-on)
D_3 partial agonism	↘ negative symptoms?	
NMDA receptors	↘ positive symptoms? ↘ cognitive symptoms? ↘ negative symptoms?	
5-HT_{2A}	= or ↘negative symptoms = or ↘cognitive symptoms	↘ prolactin elevation ↘ EPS
5-HT_{2C}		↗ weight ↘ EPS?
H_1		↗ weight Sedation
M_1		↘ EPS Dry mouth, blurred vision, urinary retention, constipation Cognitive impairment Memory problems
α1		Sedation Postural hypotension Dizziness Fatigue
hERG		QTc prolongation Torsades de pointe

EPS: Extrapyramidal symptoms

ELEMENTS AFFECTING THE CHOICE OF AN ANTIPSYCHOTIC

Considerations related to the efficacy and safety of antipsychotics are important when choosing an antipsychotic, as is the patient point of view.

Given that antipsychotics, apart from clozapine, exhibit very similar efficacy, the choice of an antipsychotic is based primarily on its tolerability and known adverse effect profile[42,62,122]. Indeed, increasing attention is being paid to the physical health of patients with schizophrenia because somatic problems and side effects, in addition to negative and cognitive symptoms, affect these patients' quality of life.

Therefore, the first choice would be an antipsychotic with the lowest side effect profile, in terms of EPS and metabolic adverse effects. FGAs are characterised by short-term (e.g. parkinsonism) and long-term (e.g. tardive dyskinesia) EPS, although they are not a homogeneous class[42]. SGAs are generally characterised by weight gain and an increased risk of metabolic syndrome, although are less discontinued than FGA[62]. In this context, aripiprazole would be a first choice of treatment due to its side effect profile and because brexpiprazole and lurasidone, the two other antipsychotics with a low risk of weight gain and EPS, are not available in Belgium. However, in situation of severe agitation, an antipsychotic with more sedative properties (i.e. H_1 and/or α_1 antagonism such as olanzapine) could be preferred over a non-sedating antipsychotic, at least temporarily, as the benefits outweigh the adverse effects[42]. In addition, other side effects could motivate the choice of an antipsychotic over another based on its potential adverse effects using its pharmacological profile, as they strongly influence treatment adherence[76].

Apart from adverse effects, in the case of treatment resistance, defined as failure to respond sufficiently to at least two adequate antipsychotic trials, clozapine is the first choice in all schizophrenia prescribing guidelines[123], as it is the only drug indicated for treatment-resistant schizophrenia (TRS) due to its greater efficacy[42,62,122]. However, careful monitoring for adverse effect of clozapine (e.g. weight gain, severe constipation) is recommended. Absolute

neutrophil counts must be monitored weekly for 18 weeks, and then every 4 weeks to prevent agranulocytosis[124].

Patients with predominantly negative symptoms may be offered cariprazine. Due to its favourable side-effect profile, with mainly akathisia, low risk of weight gain, sedation and cardiovascular side effects, cariprazine can also be proposed as first-line treatment[84,125]. Indeed, sedative side effects or severe negative symptoms affect patients' functioning and quality of life[42], and after the acute phase, it is appropriate to focus on these particular aspects[125]. However, in Belgium, cariprazine is only reimbursed in adult patients (≥ 18 years) with a diagnostic of schizophrenia for at least 2 years, without exacerbation (e.g. psychiatric hospital admission) in the last 6 months and with predominant negative symptoms (i.e. PANSS negative subscale score ≥24) for at least 6 months[126], making its use more restricted and delayed.

In addition to considerations related to efficacy or targeting of certain symptoms, the choice must also involve the route of administration. Long-acting injectable (LAI) antipsychotics outperform by up to 15% oral antipsychotic in preventing rehospitalisations, supposedly due to improved drug adherence, but also to regular contact with clinicians for administration of the injection[42]. It has also been shown to result in fewer treatment discontinuation due to lack of efficacy, which, along with reduced rehospitalisation, improves patient outcomes[127]. There are different recommendations for the use of LAIs, depending on the guidelines. Some guidelines recommend its primary use for patients with adherence issues, while others base their choice on patient preferences, and still others postulate that it should be offered after a first episode. Finally, most guidelines recommend LAIs for maintenance treatment[123]. Various barriers to the use of LAIs have been identified, from patients, prescribers and the healthcare system. Patients barriers include lack of control over medication or pragmatic inconveniences such as loss of time for regular clinic visits[128]. Prescriber barriers encompass limited experience and personal attitude, such as negative beliefs about patients' perception of LAIs (e.g. fear of needles or injection)[128], partly due to the experience of a short-acting injection during

acute decompensation[127]. Interestingly, only a small proportion of patients report fear of needles and a large majority of patients show a clear preference for LAIs when asked. In addition, most patients already receiving a LAI indicate that they would prefer to continue on it[128]. Finally, the barriers arising from the healthcare system are the pharmacy cost of these drugs and the lack of trained staff to carry out and manage the injections (e.g. monitoring the patient for 3 hours after the injection of long-acting olanzapine pamoate)[128,129]. The cost of drugs is particularly an issue in general hospitals in Belgium, where LAIs are included in the hospital's pharmaceutical package[130], which limits their start during hospitalisations, as the additional cost would be borne by the hospital. This obstacle does not exist in psychiatric hospitals, where drugs are reimbursed individually by the national health insurance[130]. It is important to highlight that up to 60% of patients are non-adherent to their treatment in schizophrenia, a figure often underestimated by clinicians. Therefore, although there were originally developed for adherence issues, LAI should now be offered to all patients as part of a shared decision making, even to supposedly adherent patients, due to their benefits over oral antipsychotics.

OTHER PHARMACOLOGICAL TREATMENT IN SCHIZOPHRENIA

Given that one third of patients do not respond sufficiently to antipsychotics, adjunctive pharmacological treatments have been tested for potential additional efficacy on the symptoms of schizophrenia. These combination strategies are not intended to target comorbid symptoms or conditions (e.g. depressive symptoms). Some pharmacological combinations with non-clozapine antipsychotics have shown statistically superior efficacy compared to monotherapy, such as lamotrigine for positive symptoms or serotonin-noradrenaline reuptake inhibitors (SNRI) for negative symptoms[131]. Only the augmentation of clozapine with glycine results in a greater reduction in positive symptoms, but no other combination with clozapine showed

superior benefit[131]. However, the quality of the included studies was quite low[131]. For example, evidence for the additional benefit of lamotrigine on positive symptoms comes from two small RCTs, with no real-world data available[132]. Because of these methodological limitations, this strategy, along with other pharmacological strategies (e.g. lithium, nonsteroidal anti-inflammatory drugs) are not recommended as adjunctive therapy in cases of insufficient response to antipsychotics[131].

Augmentation with valproate is a popular strategy, but although a 2018 meta-analysis found that this strategy created a higher clinically significant response compared to antipsychotic monotherapy, the evidence emerged from low-quality studies. Furthermore, efficacy did not persist when open-label trials were excluded. This strategy is therefore not recommended, especially given the teratogenic risk of valproate, which requires caution in the use of this drug in psychiatry[133].

Because of the high burden of disease created by negative symptoms, some psychopharmacological combination strategies have focused on these symptoms, such as adjunctive antidepressants or glycine[23]. A recent meta-analysis found superior efficacy of adjunctive SNRI or selective serotonin reuptake inhibitors (SSRI) in reducing negative symptoms, but only in studies augmenting FGA[134]. However, the effect size of these results was small and their clinical significance questionable. To date, no specific adjunctive strategy has been recommended to further reduce the positive or negative symptoms of schizophrenia[42].

Regarding mortality, it is interesting to note that adjunctive antidepressants have been associated with a reduction in deaths by suicide in schizophrenia, in a large cohort study lasting 7 years[135].

NON-PHARMACOLOGICAL TREATMENT IN SCHIZOPHRENIA: PSYCHOSOCIAL INTERVENTIONS AND ELECTRO-CONVULSIVE THERAPY

In addition to pharmacological treatment, two main non-pharmacological strategies are often used in schizophrenia: psychosocial therapies and electro-convulsive therapy (ECT).

Several psychosocial interventions are available to complement pharmacotherapy and focus on aspects of the illness other than pharmacological medication. For example, psychoeducation for patients and their relatives aims to improve adherence to treatment and the management of subsequent relapses[136]. It educates patients about treatment, diagnosis and the risk of untreated illness[122]. Psychoeducation is recommended to improve overall functioning and reduce the risk of relapse, probably by improving adherence to treatment[122]. Another therapy, cognitive remediation, aims to improve the patient's real-world skills by addressing the cognitive impairments of schizophrenia[137]. The purpose of this therapy is to improve cognitive flexibility, working memory and planning, as well as learning techniques to overcome cognitive limitations[122]. Cognitive remediation techniques can be offered in groups or online, and new digital techniques are being developed by certain pharmaceutical companies with the aim of reducing cognitive deficits and improve social functioning of patients with stable schizophrenia (e.g. CT-155 Digital therapeutic by Boehringer Ingelheim®[138,139]). However, it is currently only associated with moderate improvement in global function and a specific aspect of cognition[122]. Finally, the best-known psychotherapy with the highest level of evidence is cognitive behavioural therapy (CBT) for psychosis (CBTp). It is slightly different from CBT in that it is specifically designed for psychosis, and requires clinicians who have received appropriate training to use this therapy with people with schizophrenia. CBTp enables patients to learn the perceptions, beliefs and behaviours that may be contributing to their symptoms. In particular, it challenges hallucinations and delusions[3]. It also helps to develop coping strategies, for example for residual psychotic

symptoms, thereby reducing the level of distress[136]. CBTp also improves the level of functioning through behavioural self-monitoring techniques (e.g. task assignments or activity scheduling)[122]. Optimal patient participation often requires initial symptom reduction with pharmacology[122]. Overall, it is recommended that patients experiencing a first episode of psychosis be provided with coordinated specialty care, encompassing psychoeducation, supported employment services, family education, resiliency training and individualised medication treatment[122].

In addition to psychosocial strategies, ECT is sometimes proposed to patients with schizophrenia. Although ECT is impressively effective in cases of severe and/or treatment-resistant depression, it can also be a useful strategy in schizophrenia[140,141]. It is mainly used for patients with catatonic schizophrenia, prominent affective symptoms or neuroleptic malignant syndrome[2,140]. However, several recent meta-analyses have looked at the potential efficacy of ECT as an adjunct to clozapine or non-clozapine antipsychotics in situation of ultra-resistance (i.e. resistance to clozapine), which represents an average of 40% of TRS patients. Positive results were obtained in a recent meta-analysis, with 54% of patients achieving a response (>40% reduction in BPRS). Improvements were also seen in various areas of quality of life (e.g. satisfaction with health). However, most trials were open-label, the methodology was not very robust and the heterogeneity of the meta-analysis was high[142]. Other meta-analyses have also found significant symptomatic improvement and remission rates in clozapine and non-clozapine antipsychotics augmentation with ECT[143] but suffered from the same limitations[122]. The main issue with the methodology of trials investigating add-on ECT is that few RCTs are truly controlled, as this would require sham-ECT that creates an ethical issue of subjecting a patient to general anaesthesia without receiving the treatment[141]. Finally, the largest study to date on the long term outcomes of ECT revealed a reduced rate of psychiatric readmissions in schizophrenia inpatients treated with ECT during their index hospitalisation[141]. The most frequently reported side effects are headaches and transient memory problems[141]. In conclusion, given the

moderate quality evidence of a positive effect on patients with ultra-resistant schizophrenia, ECT may be helpful for some individuals but the potential risks and benefits must be weighted out carefully[122].

2. ANTIPSYCHOTIC POLYPHARMACY

Antipsychotic polypharmacy (APP), sometimes referred to as antipsychotic combination[144], is the concurrent use of two or more antipsychotics by one individual[42,136,145]. It is a same class polypharmacy, that may also contribute to general polypharmacy[146]. Polypharmacy is the simultaneous use of multiple medicines, with a generally accepted threshold of 5 or more medicines, although there is no standard definition[147]. The combination of clozapine with another antipsychotic is often referred to as clozapine-antipsychotic polypharmacy[148], although it is not differentiated from APP in some trials[149].

Considerations regarding the pathophysiology of schizophrenia and the pharmacology of antipsychotics described above are of great importance, along with high quality clinical evidence, to better evaluate the rationale behind the use of antipsychotic polypharmacy.

2.1. EFFICACY AND EFFECTIVENESS OVER ANTIPSYCHOTIC MONOTHERAPY

The addition of one antipsychotic to another is a widespread clinical practice[42], with the main aim of managing lack of satisfactory response to treatment.

Numerous studies have attempted to assess the superiority of APP over monotherapy in terms of efficacy. A first meta-analysis performed in 2009 sought out to compare the efficacy of APP and antipsychotic monotherapy in terms of clinically significant response, defined as a reduction ≥50% in the PANSS or BPRS scale, or a “much improved” in the CGI-I (i.e. a score of 2), but

also in terms of drop-out rates. A total of 19 studies (N=1216) were included. APP was compared equally with FGAs- or SGAs-based monotherapies. The authors were unable to assess symptoms reduction due to the lack of available data. However, they found that APP was superior to monotherapy regarding study-specific defined inefficacy and drop-out rates for any reason. Yet, the results were highly heterogeneous (I^2=78.9%), and interestingly, APP was superior to monotherapy only in the studies from China (n=7), studies lasting 10 weeks or more, co-initiation of APP (as opposed to augmentation for insufficient response), and studies comparing FGA + SGA to antipsychotic monotherapy, although it was noted that most of the latter studies (11/19) compared clozapine-antipsychotic polypharmacy to monotherapy. Finally, the funnel plot was significantly skewed in favour of positive results, suggesting a possible publication bias[149]. This was the first meta-analysis investigating this topic, but due to its limitations and the large number of additional publications on this topic, a second meta-analysis was published in 2017[150]. This analysis focused on APP augmentation strategies with efficacy as a primary outcome. Of the 22 trials included, APP with non-clozapine antipsychotics was superior to monotherapy for symptom reduction only in open-label studies (n=6) and low-quality studies (n=7), but not in double-blind studies (n=10) and high-quality studies (n=9). Clozapine augmentation with another antipsychotic, either FGA or SGA, after non-response was also not superior to monotherapy in the high-quality studies, regardless of the definition of non-response used[150]. The lack of benefit of clozapine antipsychotic polypharmacy, with the exception of combination with aripiprazole, for resistant schizophrenia has been confirmed in other meta-analyses[151,152]. Study-defined response (i.e. ≥20% PANSS/BPRS reduction, ≥25% PANSS reduction, or ≥20% PANSS reduction or CGI-I 1 or 2) was again not superior in the APP augmentation arm in high quality and double-blind studies[150] . For negative symptoms, the addition of a partial agonist (i.e. aripiprazole) to an antagonist resulted in improvement, but the combination of two D_2 antagonists did not. However, there was no comparison between the strategy of switching to a partial agonist and that of adding a partial

agonist. Finally, the depressive symptoms did not differ between APP and monotherapy. Interestingly, patients receiving a higher dose of APP improved the least compared to monotherapy, which may be explained either by the fact that APP is less effective in more severe patients, or by the fact that patients have secondary negative symptoms due to significant D_2 receptors blockade, which impedes symptom improvement. Unlike the previous meta-analysis, the funnel plot did not indicate possible publication bias and heterogeneity was reduced by the inclusion of efficacy-focused trials and by the mean of sub-analyses (e.g. double blind versus open label, region)[150]. This difference between open-label and blinded trial suggests that patient and clinician expectation bias may account for much of the improvement seen in patients in clinical practice.

Following this meta-analysis showing no improvement in efficacy when using APP as augmentation strategies, thus confirming the recommendations made by clinical prescribing guidelines[42], some authors suggested that, since APP was used to treat refractory illness, its perceived efficacy could be falsely diminished. Conversely, another criticism was that patients who agreed to take part in RCTs were less severely ill, although this was not confirmed in the previous meta-analysis where baseline PANSS/BPRS scores did not influence study results. Finally, as data emerged only from clinical trials, there was a lack of real-world data to assess the effectiveness of APP in everyday clinical practice.

To answer these interrogations, a large Norwegian cohort study was conducted and published in 2019, measuring psychiatric rehospitalisation after hospital discharge, and all-cause hospitalisations as a primary outcome. Follow-up began in 1996 and ended in 2015, with a median duration of follow-up of 14 years. To avoid residual confounders, within-individual analyses were performed. In this cohort of 62 250 patients, the combination of clozapine and aripiprazole led to a greater reduction in the risk of psychiatric rehospitalisation than clozapine alone (Hazard Ratio [HR]=0.86, 95% confidence interval [95% CI] =0.79-0.94). The risk of psychiatric rehospitalisation and all-cause hospitalisation did not differ between all other APP and the monotherapy with the most effective antipsychotic in the

combination. Similar results were obtained with other combinations with clozapine[153]. This indicates that, beside the combination of clozapine and aripiprazole, APP did not provide any benefit compared to monotherapy. Interestingly, the combination of clozapine and aripiprazole has already shown higher efficacy in a previous meta-analysis[151]. However, no information on quality of life or level of functioning was available.

In the same year, another cohort study was published in the UK. Among 17 255 outpatients followed for an average of 5.7 years, no difference was observed between APP and monotherapy in terms of risk of unplanned hospital admission (HR=1.14; 95% CI=0.98–1.32), emergency room visit (HR=0.95; 95% CI=0.80–1.14), and death (HR=1.02; 95% CI=0.76–1.37)[75].

Moreover, a cohort study of 5523 adults showed that patients on APP had a higher risk of being readmitted to hospital within the 6 months following discharge than patients discharged on monotherapy (HR = 1.4, 1.2–1.7, $p < 0.001$). Similar results were obtained for patients discharged on clozapine-antipsychotic polypharmacy compared with patients on clozapine monotherapy (HR = 1.8, 1.2–2.6, p = 0.008), even after adjusting for potential confounders (e.g. service use in the 6 months prior to index hospital discharge).[154]

These real-world studies demonstrate that APP does not modify healthcare utilisation compared to monotherapy over the long term, which, in addition to not improving symptoms, suggests that APP does not improve patient outcomes compared with monotherapy. The latter cohort even suggests a higher risk of short-term hospital readmission after discharge.

Finally, it is important to note that APP has never been directly compared with switching to clozapine. Only observational data exists, and indicates that clozapine is superior to APP in reducing psychiatric rehospitalisation[74], which is understandable from a pharmacological point of view. Indeed, the use of multiple drugs with the same target (i.e. D_2 receptors) is expected to be less effective than a drug with a different mode of action (i.e. D_2 and glutamatergic receptors) and greater efficacy than other antipsychotics, as described above.

Last but not least, some studies have attempted to investigate patient symptoms (i.e. PANSS/BPRS) and side effects following the switch to antipsychotic monotherapy versus staying on APP, in patients who have been stable on APP. Only 6 studies have been published, described in a 2019 meta-analysis. The studies were of low to very low quality, mainly because only 2 were double-blind, the others were either rater-blinded only (n=3) or open-label (n=1). The patients included had been ill for at least 3 months in 3 studies, for two months in one study and chronically but severely ill in one study. The last study did not describe the type of severity of illness. All studies compared switching to monotherapy versus staying on antipsychotic polypharmacy. Five of the six studies gradually discontinued the antipsychotic for the monotherapy group over a period of at least 4 weeks (up to 12 weeks). They used efficacy scores such as PANSS, and/or BPRS and side-effect scores. The studies lasted between 4 weeks and 6 months, an appropriate duration since efficacy/lack of efficacy can be detected very quickly, as described previously. However, most studies were small, different combinations were compared (i.e. antipsychotic polypharmacy with and without clozapine), and the APP was not clearly defined, i.e. whether or not it included low-dose antipsychotics, except in one study where it was clearly stated that patients receiving quetiapine<100 mg were excluded. This meta-analysis showed that there were more drop-outs from all causes in the monotherapy groups, but that drop-outs due to lack of efficacy or side-effects were similar between the two groups. In addition, PANSS and/or BPRS scores were similar, as were CGI and global cognitive function (composite score), except in the last study where the switch to monotherapy led to an improvement in attention and executive function[155].

2.2. ADVERSE EFFECTS AND POTENTIAL HARMS

Like general polypharmacy, APP has long been suspected of increasing rates and burden of adverse effects. However, there is little or no data for some effects, and inconsistent data for others. Nevertheless, certain side effects have been found to be more frequent in patients treated with APP.

EXTRAPYRAMIDAL SYMPTOMS

The most common adverse effect associated with APP is increased rates of extrapyramidal symptoms (relative risk=1.43)[146,156] and higher likelihood of prescription of anticholinergic drugs[157]. This risk has been found not only in APP with FGAs but also in APP with SGAs[158]. However, as APP is also associated with a high total dose of antipsychotics[146], it is likely that EPS are caused by cumulative blockade of D2 receptors, exceeding the 80% blockade threshold, where even the putative protective effect of $5HT_{2A}$ blockade is no longer protective[158].

HYPERPROLACTINEMIA

In addition, APP has also been associated with a greater elevation of prolactin[150], including in APP with antipsychotic with a low impact on prolactin levels such as olanzapine or quetiapine[157]. Consequently, APP with SGA was associated with a higher rate of sexual dysfunction[157,159]. The only exception is the addition of aripiprazole, which reduces hyperprolactinemia induced by other antipsychotics. The optimal dose of aripiprazole to use is probably 5 mg/day[160]. A dosage of 10 mg/day has been shown to reduce the prolactin levels to a greater extent than a dose of 5 mg, but doses higher than 10 mg do not provide additional benefit[160]. However, at higher doses, due to aripiprazole's high affinity for the D_2 receptors[76,161], it will displace the other antipsychotics from D_2 receptors, rendering the latter useless. Concerns have also emerged about the potential risk of schizophrenia decompensation with the addition of aripiprazole, but this was not confirmed in a meta-analysis of randomised controlled trials, where PANSS and BPRS scores remained similar in the placebo and aripiprazole groups[160]. However , if a higher dosage of aripiprazole is required to reduce hyperprolactinemia, as it will displace the other antipsychotic from D2 receptors, and because of the similar efficacy of all antipsychotics, it would be wiser to switch to aripiprazole rather than adding it to another antipsychotic.

As elevated prolactin is associated with decreased bone mineral density, and as antipsychotics can cause postural hypotension by α_1 receptors blockade

and sedation through H_1 receptors blockade, it has been suggested that they may increase the risk of hip fracture as a long-term effect. This hypothesis was confirmed in a Danish cohort of 15 431 patients with schizophrenia, where APP increased the risk of hip fracture compared to antipsychotic monotherapy[162].

ANTICHOLINERGIC EFFECTS

APP with SGAs also increases the risk of anticholinergic side effects, such as dry mouth and constipation, with a Number Needed to Harm (NNH) of 4 and 11 respectively[159]. Although these effects may not be taken very seriously, it should be noted that ileus is responsible for more deaths due to clozapine than agranulocytosis[163]. In addition, dry mouth has been cited as one of the top three side effects patients struggle with[164].

COGNITIVE IMPAIREMENT

Cognitive impairment is one of the symptoms that most affects the social function and quality of life of individuals living with schizophrenia[137]. APP has been shown to further reduce cognitive performance and scores to a greater extent than monotherapy[145], especially in visual memory, recall, performance IQ (Intelligence quotient) and executive function[165]. This effect is probably due to excessive dosing, i.e. when the patient receives more than 1000 mg chlorpromazine equivalent per day and is unlikely to be influenced by the severity of psychotic symptoms[165]. Moreover, switch to monotherapy has been shown to improve attention and processing speed, although these data emerged from a study in which only the raters were blinded[166].

CARDIOVASCULAR ADVERSE EFFECTS

- Weight gain and metabolic syndrome

APP has been associated with weight gain in several studies[164,167]. The addition of aripiprazole to clozapine[157,168] or olanzapine[169-171] is an exception, but the data are from small and open-label studies, and daily dose of clozapine was subsequently reduced by up to an average of 20% in one study. Indeed, a recent meta-analysis showed that weight gain induced by

antipsychotics is dose-dependent[172]. In addition, weight loss was seen when switching to aripiprazole based on stronger data[173]. Besides, APP has also been associated with higher rates of metabolic syndrome and dyslipidemia[174]. Children and adolescent exposed to APP were found to be at higher risk of developing type II diabetes, obesity and dyslipidemia[167]. Finally, in a large cohort of 345 937 patients, the incidence of diabetes was significantly higher in patients taking APP[175].

- Cardiac effects

APP has been associated with higher risk of QTc prolongation in women compared to monotherapy[176]. Moreover, APP increases the likelihood of cardiovascular events such as myocardial infarction, ischemic heart disease, or arrhythmias[167]. Numerous small studies from the past two decades have warned of increased mortality with APP[177,178], but two large cohorts eventually found no increased risk of death with APP[75,121].

SIDE EFFECT BURDEN

Finally, the overall burden of side effects appears to be higher in patients on APP than in patients on antipsychotic monotherapy[157]. The addition of low-dose antipsychotics may be considered safer, but a recent cohort found that low-dose quetiapine increased the risk of major cardiovascular events[179]. Consequently, adding one antipsychotic to another, even at low dose, probably also increase the risk of side effects.

2.3. REASONS FOR USING ANTIPSYCHOTIC POLYPHARMACY IN SCHIZOPHRENIA AND RECOMMANDATIONS

Many reasons for using APP have been identified, although not in Belgium.

IMPROVING OUTCOMES

A major reason for using APP is to try to reduce psychotic symptoms, improve outcomes, or speed up effect [180-184]. Indeed, some clinicians report using APP to ensure timely hospital discharge[185]. Interestingly, improvement after the

addition of a second antipsychotic may be due to the first antipsychotic having been used for longer, especially in acute setting when polypharmacy is often used very early after hospital admission[184]. Indeed, an early response can be assessed after no more than 2 weeks of treatment[63-65], and if a second antipsychotic is added after a few days, efficacy may be wrongly attributed to the combination rather than to sufficient duration of use of the first antipsychotic[184]. Many patients are therefore left on APP for fear of symptomatic decompensation, or because it is believed that monotherapy has not been sufficient to prevent relapses[183,186]. However, as shown above, none of these effects can be achieved by using APP instead of monotherapy.

APP is also sometimes used after a lack of response to two or more antipsychotics, which delays the introduction of clozapine[184,187], but also after a lack of response to clozapine (i.e. ultra-resistance). In the latter situation, as indicated above, there is no evidence of superior efficacy in combining another antipsychotic with clozapine, except perhaps with the addition of aripiprazole[150,153]. Clozapine antipsychotic polypharmacy is probably a strategy of last resort, but with the risk of increasing adverse effects, such as metabolic syndrome or anticholinergic side effects, while failing to improve patients' symptoms. In these situations of ultra-resistance, greater emphasis should be placed on quality of life and optimising patient functioning, especially when symptoms are still very much present under clozapine antipsychotic polypharmacy.

PHARMACOLOGICALY SOUNDED

The main reason underlying the belief that APP would lead to greater efficacy or a faster onset of action is the optimisation of D_2 receptors occupancy or activity at other receptors such as serotonin or adrenergic receptors[184]. Indeed, one justification often given is the use of APP because antipsychotics have a different pharmacology[182] or different pharmacological mechanisms[181]. Moreover, the combination of an antipsychotic with a low affinity for D_2 receptors, i.e. a high Ki (e.g. quetiapine)[76,161] with an antipsychotic with a higher affinity for the D_2 receptors (e.g. haloperidol,

risperidone)[76,161] is often considered to optimise D_2 receptor occupancy[146], potentially leading to greater therapeutic potential (e.g. acceleration or enhancement of effect)[181,182,184]. However, except for clozapine, all antipsychotics achieve D_2 occupancy of at least 60-65% at therapeutic dose[77,78,80]. The only combination that might justify this strategy is the addition an antipsychotic to clozapine, which only blocks 40-50% of D_2 receptors at therapeutic dosage[80,96], but this has only been verified with amisulpride augmentation of clozapine[146], but without benefit on symptoms[188]. In addition, the second strategy of reaching different receptors (e.g. 5-HT_{2A} or H_1) is also unwise because the receptors other than D_2 that are blocked by all current antipsychotics are not linked to the efficacy of antipsychotics, but rather to their side effects, which would lead to more side effects as mentioned previously.

MANAGEMENT OF A COMORBID CONDITION OR A SPECIFIC SYMPTOM

Clinicians may wish to target a comorbid condition, such as substance use disorder and intellectual disability, with another antipsychotic[181-184]. The main problem with comorbid substance use is the reduced efficacy of antipsychotics, leading to more severe positive symptoms, poorer adherence, higher relapse rates[189] and a higher risk of aggression[184]. However, no superiority of one antipsychotic over another has been demonstrated in reducing substance use[42], so it is recommended to follow the schizophrenia guidelines[189]. In addition, APP is often use in the context of persistent aggression or agitation, especially in forensic services to reduce the risk of violence[184]. However, few pharmacological options have high-quality evidence for the management of behavioural problems in schizophrenia. First-line management should focus on ensuring adherence to the antipsychotic, as improved symptom control appears to reduce levels of aggression, probably through the reduction of paranoid delusions and command auditory hallucinations[42]. Although naturalistic studies have shown SGAs to be more effective than FGAs in reducing violence, these results were not confirmed by a large RCT, showing that antipsychotics appeared to have similar efficacy in reducing violence over a 6-months period[190]. In addition,

clozapine was found to have the greatest efficacy on aggression, but it is unclear whether this effect is related to the greater efficacy of clozapine or to an independent antihostility effect[42,184]. Nevertheless, high dose of antipsychotics has not been associated with a reduction in aggression in acute care settings, and APP is therefore not recommended for the purpose of further blocking the D_2 receptors[42].

INSOMNIA

Off-label use of antipsychotics may lead to APP, especially the use of low-dose antipsychotics as hypno-sedatives, in order to reduce the use of benzodiazepines[185]. However, as noted above, the use of low doses of quetiapine has been linked with higher risk of major cardiovascular events[179]. In the case of a comorbid sleep disorder, a sedative antipsychotic should first be used as monotherapy as the main treatment for schizophrenia, and the time at which it is taken should be optimised (i.e. at bedtime).

INERTIA OF PRACTICE

It is interesting to note that an important reason for the use of APP is that it is inherited from and/or recommended by other clinicians, with or without benefit[180,182]. This reason therefore encompasses the inertia of practices but also the influence of social relationships on prescribing behaviour.

IMPROVING TREATMENT ADHERENCE

Another justification sometimes mentioned, by 30% of prescribers, is that the patient is non-adherent[186]. This could be understood in different ways. Either it is thought that the patient will take at least one antipsychotic, or that the increased control of their symptoms will enable them to take their medication appropriately. However, the complexity of the medication regimen, but also the side effects, are associated with poorer adherence, which has led to the recommendation that APP should not be used to improve adherence to antipsychotics in schizophrenia[42]. Interestingly, APP is also used after relapse, when it is unclear whether the relapse is due to non-adherence or a real lack of response. This could lead to the prescription of polypharmacy to a patient who was in fact non-adherent[185]. Adherence

should be verified using therapeutic drug monitoring and switch to an LAI should be considered when adherence issues have been identified[42].

PATIENT OR FAMILY BARRIERS

The "patient does not want to change" or the family are also mentioned as reasons for leaving a patient on APP. However, no study has investigated patient's opinion on APP. It is difficult to say whether this is the result of real shared decision-making about patients' wishes, or whether it is the result of inertia of practice while appearing to adopt good practices, as suggested by some authors[186].

2.4. COMMENTS REGARDING THE USE OF ANTIPSYCHOTIC POLYPHARMACY

With limited options available in the absence of a sufficient response, APP is often used in an attempt at improving outcomes. However, due to increased side effects and worsening cognitive function, psychosocial functioning is likely to be affected by this increased medication burden. In addition, APP is frequently used as initial treatment without a prior trial of antipsychotic monotherapy, and the majority of patients are being prescribed APP within 90 days following initiation of any antipsychotic[191]. The use of APP has also been shown to delay the start of clozapine[191], the only available option in situation of treatment resistance. As patient's safety is one of the World Health Organisation top priority, particularly through the reduction of polypharmacy[147], an in-depth understanding of the causes of poor response to treatment could therefore be an option for limiting the use of APP in schizophrenia.

3. EXPLORING REASONS OF POOR TREATMENT RESPONSE OR LACK OF TOLERABILITY

About a third of patients are treatment resistant, that is an absence of adequate response to at least two antipsychotics. However, about 30% of these patients have low or undetectable plasma concentrations of their antipsychotics[192,193]. In addition, other factors can lead to poor response to antipsychotics, and will be detailed thereafter.

3.1. POOR TREATMENT-ADHERENCE

Poor treatment-adherence, whether intentional or unintentional, is an important challenge in the management of schizophrenia[194]. Maintaining adherence over time is even more difficult, with an estimated 36% experiencing poor adherence each year of treatment[194].

Reasons for unintentional non-adherence include factors that affect the ability to take medication regularly, such as substance abuse that worsens the patient's psychopathology, cognitive impairment, and lack of family or social support[194].

Patients' attitude to medication, which reflects their perceived benefits of medication against adverse effects, greatly influence intentional adherence to treatment. A positive attitude would mean, for example "my thoughts are clearer on medication", while a negative attitude would be reflected, for example, by "'I feel weird, like a zombie, on my medication". Patients with a greater awareness of their mental illness (i.e. insight), who believe that medication alleviates symptoms and who are more aware of the social consequences of a mental disorder are more likely to have a positive attitude towards medication. Inversely, patients with more deficit, negative, positive and depressive symptoms, as well as higher psychopathological scores, are more likely to have a negative attitude towards medication[195].

In addition, medication side effects, such as dyskinesia or sedation, are major causes of poor attitude toward medication and therefore intentional poor adherence[194,196].

Lack of insight is strongly associated with a shorter duration of antipsychotic treatment and a greater odds of drug discontinuation and psychiatric hospitalisation[197]. However, a meta-analysis found that psychosocial intervention alone (i.e. education about the illness) failed to influence medication adherence. Attitude towards medication, i.e. perceived need and concerns, was found to be a dimension distinct to insight that better predicts medication adherence, leading to recommendations to focus intervention on attitude towards medication in addition to education about the illness.[198]

Despite this, clinicians tend to overestimate patient adherence. One study using microelectronic monitoring system that records the time and date the pillbox is opened found that nearly 62% of the patients were poorly adherent, described as missing more than 30% of their medication, while only 5.3% were correctly identified by clinicians[199]. In another study using pharmacy claims to monitor adherence, 94% of patients with poor adherence (taking less than 30% of their medication) were wrongly considered by their physician to be well adherent[200].

Unrecognised poor adherence can lead to unnecessary dosage increases, medication switches or polypharmacy[200].

3.2. PHARMACOKINETIC VARIABILITY

Several situations can modify the plasma concentration of antipsychotics, leading to increase in side effects or a lack of response.

DRUG-DRUG INTERACTIONS

The best-known pharmacokinetic modifiers are drug-drug interactions. Antipsychotics, which are substrates of Cytochrome P450 (CYP), chiefly CYP3A4, CYP1A2, CYP2D6, and CYP2C19, but also UDP-

glucuronosyltransferases (UGT)[82], are frequently co-prescribed with other drugs that inhibit or induce their metabolism. Not all interactions have a clinically significant effect, however, the combination of several low-potency inhibitors or inducers may result in a clinically significant adverse effect or lack of efficacy. It is often accepted that a change in the antipsychotic concentration/dose ratio (i.e. C/D) of a factor 2 is clinically meaningful[201].

Some interactions will be described in a non-exhaustive manner below, with a focus on the most clinically relevant interactions with the most frequently prescribed antipsychotics.

Risperidone is mainly metabolised by the CYP2D6 and, to a lesser extent by the CYP3A4[201] (Table 7). Its active metabolite, 9-hydroxyrisperidone or paliperidone, is also active and has a plasma concentration approximately 22 times higher than that of risperidone[202]. Due to the short half-life of risperidone (i.e. 3 hours), the effect is mainly mediated by 9-hydroxyrisperidone. For this reason, plasma concentration of the total active moiety (i.e. risperidone + 9-hydroxyrisperidone) must be monitored as part of therapeutic drug monitoring (TDM)[202]. The impact of CYP inducers on the response to risperidone is unclear and debated, as it will result in a greater synthesis of 9-hydroxyrisperidone, which is mainly eliminated unmetabolized. However, a threshold of 74 ng/mL of risperidone was found to significantly increase the risk of EPS, which would therefore mean that strong CYP2D6 and 3A4 inhibitors are likely to increase the risk of side effects[202]. For example, levomepromazine, an antipsychotic often co-prescribed at low doses as a hypno-sedative with other antipsychotics, is a CYP2D6 inhibitor (table 8). In situations where the patient is also being prescribed paroxetine or fluoxetine, this can increase the plasma concentration of risperidone by up to 7-fold[201], thereby greatly increasing the risk of EPS.

Table 7. Average half-life and enzymes and transporters involved in antipsychotic pathways

Antipsychotics	t½ (hours)	Enzymes and transporters affecting the antipsychotic
Aripiprazole	70	**CYP2D6, CYP3A4**, P-gp
Bromperidol	20	**CYP3A4**
Cariprazine (+ N-desmethylcariprazine + N-didesmethylcariprazine)	44 (+37 +446)	CYP2D6, **CYP3A4**
Clozapine	12	**CYP1A2, CYP2C19**, CYP3A4, P-gp
Haloperidol	18	**CYP2D6, CYP3A4**, AKR, UGT, P-gp
Olanzapine	33	**UGT1A4**, UGT2B10, FMO, **CYP1A2**, CYP2D6, P-gp
Paliperidone	20	60 % excreted unmetabolized, CYP3A4, UGT, P-gp
Quetiapine	8	**CYP3A4**, CYP2D6, P-gp
Risperidone (+ 9-OH-risperidone)	3 (+20)	**CYP2D6**, CYP3A4, P-gp
Sertindole	73	**CYP2D6**, CYP3A4
Zuclopenthixol	18	**CYP2D6**

t1/2: average elimination half-life; CYP: cytochrome P450; P-gp: P-glycoprotein; AKR: aldo-keto reductase; UGT: UDP-glucuronosyltransferase; FMO: Flavin monooxygenase
Strong or moderate drug interaction that affects the enzymes indicated in bold will lead to a significant increase or decrease in the plasma concentration of the substrate drug.

Olanzapine has several routes of metabolism, but UGT1A4 and CYP1A2 are the two main ones (Table 7). Its therapeutic range is between 20 to 80 ng/mL[82]. Concomitant administration of carbamazepine, which induces both

enzymes, leads to a decrease in olanzapine plasma concentration of up to 71%, while the co-administration of fluvoxamine, a CYP1A2 inhibitor (table 8), increases its level by up to 2-fold[201]. Not all olanzapine-related adverse effects are dose-dependent, but co-administration with potent CYP1A2 or UGT1A4 inhibitors may result in increased sedation, postural hypotension, tachycardia, transaminase elevation and seizures[203]. Elevated plasma concentrations may also be associated with clinically relevant anticholinergic side effects and may impair cognitive functioning. The combination of olanzapine and fluvoxamine has also been shown to increase the QTc interval[203]. Finally, smoking induces the CYP1A2, resulting in lower-than-expected plasma concentrations of olanzapine in smokers, or a rapid increase in olanzapine concentration if smoking is abruptly stopped. Smoking status appears to account for about 25%-30% of the variability in olanzapine plasma concentration[204], meaning that 10 mg in smokers would correspond to 7 mg in non-smokers[205], irrespective of other sources of variabilities. Smoking status is very important to consider, as it affects about 70% of patients with schizophrenia[206], which is much higher than in the general population in Belgium (around 15%)[207]**.** It has been shown that at least 10 cigarettes a day are required to reach a significant induction of CYP1A2, and that CYP1A2 activity returns to normal within 3 to 4 days after smoking cessation[82].

Aripiprazole is metabolised by CYP3A4 and CYP2D6, and its plasma concentration is significantly affected by strong inducers or inhibitors of these CYPs (table 7). For example, co-medication with carbamazepine reduces its concentration by up to 88%, while co-medication with CYP2D6 inhibitors (e.g. levomepromazine and fluoxetine, see table 8) increases its concentration by up to 44%[201]. This may lead to an increased risk of akathisia, evidenced in studies showing a higher rate of akathisia in patients co-medicated with antidepressants[203].

Clozapine has several metabolic pathways, as does olanzapine, although its main pathways are mediated via CYP1A2 and CYP2C19, and to a lesser extent CYP3A4[201], particularly in patients with reduced CYP1A2 activity[208] (table 7). Its main metabolite, norclozapine, does not appear to have an antipsychotic

effect, although it may cause anticholinergic, hypersalivation and cardiac side effects. Smoking, by inducing CYP1A2, reduces the plasma concentration of clozapine by up to 50%[205], making it necessary to double the dose of clozapine in smokers. In addition, the antidepressants fluoxetine, fluvoxamine and paroxetine double the plasma concentration of clozapine (table 8), increasing the risk of dose-related side effects such as sedation, hypotension and seizure [201-203].

Table 8. Major inhibitors and inducers of enzymes involved in the metabolism of antipsychotics

	Drug significantly inhibiting the enzyme	Drug significantly inducing the enzyme
CYP1A2	**Fluvoxamine, ciprofloxacin,**	Carbamazepine, **smoke**
CYP2D6	**Bupropion, fluoxetine, levomepromazine, mirabegron, paroxetine**, amiodarone, citalopram, clomipramine, duloxetine, escitalopram, fluvoxamine, sertraline, venlafaxine	/
CYP3A4	**Ciprofloxacin, clarithromycin, diltiazem, erythromycin,** amiodarone, fluconazole	**Carbamazepine, rifampicin, St John's Wort (hypericum),** ethanol, oxcarbazepine, phenobarbital, phenytoin
CYP2C19	**Fluconazole, fluvoxamine,** fluoxetine, topiramate	**Phenobarbital, phenytoin, rifampicin**

UGT: UDP-glucuronosyltransferase; Drug in bold are strong inhibitors or inducers

PREGNANCY

Pregnancy can lead to an apparent poor response. Indeed, in addition to well-known drug interactions, pregnancy also affects the pharmacokinetics of antipsychotics. The activity of CYP2A6, 2C9, 2D6 and 3A4, UGT1A4 and

UGT2B7 increases, while the activity of CYP1A2 and CYP2C19 decreases[209]. In addition, hepatic blood flow increases, which further enhances the metabolism of certain drugs or balances the inhibition of CYPs for other drugs. Moreover, glomerular filtration rate increases by up to 50% in pregnant women[209].

Few data are available on the significance of these pharmacokinetic variations, but a recent study showed that the serum concentration of quetiapine and aripiprazole fell by up to 50% during pregnancy. This is probably due to the combined effect of increased hepatic blood flow and enhanced activity of CYP3A4 and CYP2D6, the two CYPs that metabolise these antipsychotics. After delivery, plasma concentrations of aripiprazole have been shown to return to baseline within 2 to 3 weeks. Conversely, the serum concentration of olanzapine does not appear to be affected by pregnancy, supposedly due to the balance between increased UGT1A4 activity and decreased CYP1A2 activity, the two major metabolic pathways of olanzapine[210]. As the effect in pregnancy depends not only on the antipsychotic used, but also on cofactors such as comedication used during pregnancy, it is recommended to monitor the plasma concentration of antipsychotics metabolised by these CYPs or UGTs once per trimester and within 24 hours after delivery[82].

3.3. GENETIC POLYMORPHISM

In addition to pharmacokinetic interactions through inhibition or induction of metabolising enzymes or transporters, genetic variants affecting these proteins may also be responsible for particularly low or high plasma concentrations of antipsychotics. Plasma concentrations outside therapeutic ranges may be the cause of a poor response to antipsychotics or particularly severe side effects, both of which are risk factors for poor compliance, inappropriate switching or the use of antipsychotic polypharmacy. The absence of a response or the presence of a specific side effect may also be

due to a variant affecting the drug's targets. Pharmacogenetics is therefore the study of how a patient's genetics change their response to medicines[211].

In order to select an antipsychotic at the right dose, it is necessary to know not only the pharmacology of the antipsychotics and co-prescribed drugs, but also the characteristics of the patients[212]. Some genetic variants affecting the antipsychotics most frequently prescribed in Belgium are described below.

VARIANTS AFFECTING PHARMACOKINETICS OF ANTIPSYCHOTICS

- Risperidone

As described in the previous section, risperidone is extensively metabolised by CYP2D6 and CYP3A4/5 into its active metabolite 9-hydroxyrisperidone, also known as paliperidone[201], which has a plasma concentration approximately 22 times higher than that of risperidone[202]. Since risperidone has a short half-life of around 3 hours, the effect is mainly mediated by 9-hydroxyrisperidone which exhibits a longer half-life of about 20 hours[82]. CYP2D6 accounts for up to 65% of the variability in risperidone metabolism[213], and genetic polymorphism of *CYP2D6* has been shown to significantly affect risperidone plasma concentration[214]. According to the *CYP2D6* genetic profiling, patients can be classified into different categories, defined by the so-called activity score (AS). Accordingly, patients are classified as poor metabolisers (PM, AS=0) which represent around 6% of the Caucasian population[214], intermediate metabolisers (IM, AS = 0.25-1), normal metabolisers (NM, AS=1.25-2.5), and ultra-rapid metabolisers (UM, AS >2.5), the latter having multiple copies of the gene that leads to increased metabolism[215]. Four polymorphisms (*3, *4, *5, and *6) account for 98% of inactive alleles[216]. The area under the concentration-time curve (AUC) of risperidone is about 8 times higher in CYP2D6 PM and 1.8 times higher in IM than in NM[217]. As a threshold of 74 ng/mL was found to significantly increase the risk of EPS[202], CYPD6 PM or IM are therefore likely to be at increased risk of these side effects if the increase in concentration reaches the EPS threshold[218]. In addition, the ratio risperidone/9-hydroxyrisperidone is shifted toward more risperidone in PM, and risperidone crosses the blood-

brain barrier more efficiently than 9-hydroxyrisperidone, which may further increase the risk of central side effects such as EPS[213,219]. This was confirmed in children, where PM and IM were at greater risk of side effects and EPS[220], but also in adults, were more tremor and akathisia was seen in patients with a higher Cmin of the active moiety (i.e. risperidone + 9-hydroxyrisperidone)[217]. Besides, PM and IM were also found to have higher prolactin levels[217]. Finally, a recent cohort study showed that PM had an increased risk of treatment failure which could be due to poor treatment adherence caused by significant side effects[219]. On the basis of this cohort study, the Dutch Pharmacogenetic Working Group (DPWG) recommends using 67% of the dose of risperidone in PM, and in the event of problematic neurologic side effects, to reduce the dose by up to 50%[215]. No recommendations have been made by the Clinical Pharmacogenetics Implementation Consortium (CPIC).

Conversely, the impact of CYP2D6 UM on the efficacy of risperidone is debated, as 9-hydroxyrisperidone and risperidone show similar efficacy, and small size studies found no difference between UM and NM in terms of efficacy. However, a recent cohort study showed that UM were more likely to have treatment failure, defined as being switched to another antipsychotic within one year[219]. This effect is probably due to the change in the risperidone/9-hydroxyrisperidone ratio towards more 9-hydroxyrisperidone which crosses the blood-brain barrier less effectively. For that reason, the DPWG recommends choosing an alternative drug or to titrate the dose based on the maximum dose for 9-hydroxyrisperidone in *CYP2D6* UM[215].

Last, the impact of *CYP3A* polymorphism on risperidone plasma concentration is controversial, with one study showing that CYP3A5 non expressers have a higher plasma concentration of the active moiety[220], and another that carriers of at least one *CYP3A4*22* allele (i.e. reduced expression) have a decrease in risperidone clearance but no significant effect on its plasma concentration[217]. In addition, other researchers found no impact of *CYP3A* polymorphism on risperidone plasma concentration[221] or on the daily dose prescribed[222]. No impact on efficacy has been demonstrated in

quality studies, and due to the likely lack of significant impact on the pharmacokinetics of risperidone and prescribed daily dose, no dose adjustment regarding *CYP3A* genetic polymorphism is recommended by the DPWG[215], and no recommendation have been stated by the CPIC. It is likely that no clinically meaningful effect was seen, as a change in concentration/dose ratio (i.e. C/D) of a factor of 2 is generally considered clinically significant[201], and CYP3A4 is a minor metabolising pathway of risperidone.

- Olanzapine

Olanzapine is mainly metabolized by UGT1A4 and CYP1A2, and to a lesser extent by CYP2D6 and CYP3A4[82].

Olanzapine undergoes predominantly direct glucuronidation by UGT1A4. UGTs are a family of enzymes that catalyse the conjugation of glucuronic acid to many drugs, such as olanzapine, thereby increasing their hydrophilicity and allowing them to be eliminated by the bile or urine [223]. Although around a hundred SNPs have been identified in *UGT1A4*, around ten of them are linked to an amino acid change [223]. Among them, *UGT1A4*3* (rs2011425), present in 2.6 to 9% of the Caucasian population, is associated with higher glucuronidation activity [223,224]. Some studies have shown that *UGT1A4*3* carriers, whether homozygous or heterozygous, exhibit increased formation of the glucuronide metabolite of olanzapine, but with no change in the concentration of olanzapine (parent drug)[225 226 227], while others have shown that *UGT1A4*3* was associated with a 25% reduction in plasma olanzapine concentration[228]. One study which looked only at olanzapine plasma concentration without measuring its glucuronide metabolite found that *UGT1A4*3* carriers had non-significant lower plasma concentrations, but one limitation was the absence of *3/*3 homozygotes in their cohort[229]. Finally, regarding tolerability, a recent study of 91 schizophrenic patients treated with olanzapine monotherapy showed that *UGT1A4*3* was associated with a lower severity of autonomic nervous system dysfunction[224], assessed by measuring heart rate variability at rest, which is interesting because

autonomic nervous system dysfunction is associated with sudden death due to cardiovascular disease[224]. Interestingly, the combined effect of *UGT1A4* genetic polymorphism, sex and smoking status appears to have up to a 5-fold impact on olanzapine plasma concentration[228].

The influence of *CYP1A2* polymorphism on the pharmacokinetics and efficacy of olanzapine is controversial and remains unclear. As *1F is the most common variant in Europe (minor allele frequency (MAF): 0.68), the DPWG makes no recommendation regarding olanzapine dose adjustment in patients with the *CYP1A2*1F/*1F* genotype[215]. However, some studies have found a lower dose-corrected olanzapine plasma concentration in *CYP1A2*1F* homozygous patients compared with *CYP1A2*1F/*1A* patients when adjusted for potential confounders (e.g. age, sex and/or weight) [229-231], but a large cohort study of 342 Caucasians did not[232]. The latter study, however, included patients on long-term olanzapine, which may induce a recruitment bias towards more patients with a good response and/or tolerance, as the others are more likely to have been switched to another antipsychotic[232]. In addition, some studies have shown that *CYP1A2*1A/*1F* genotype correlates with better response [230,231], while others have not[229]. As the difference in plasma concentration between *CYP1A2*1F/*1F* and *CYP1A2*1F/*1A* genotypes is between 7%[231] and 22%[230], the DPWG suggests that this is unlikely to be clinically significant, and if it increases the chance of a better response, there is no need to recommend dose adjustment[215]. Regarding adverse events, some studies found no impact of *CYP1A2* polymorphism on the risk of side effects, but it should be noted that some of them did not use side effect scales but relied on self-reported adverse events[229,233] which are known to be underreported in schizophrenia. Others have only used EPS scales[234] which are uncommon with olanzapine, making it impossible to detect other common side effects such as anticholinergic effect, dizziness, constipation or sedation. Regarding other *CYP1A2* variants, one study showed that *CYP1A2*1D*, delT/delT genotype carriers had 2.3 higher dose-corrected plasma concentrations[229], but a recent study in non-smokers found no association between *CYP1A2*1C, *1F* and *1B* and olanzapine exposure,

although the frequency of homozygous patients was not described, making interpretation of these results more difficult[233]. However, many other studies have found no association between *CYP1A2*1C* and olanzapine side effects [224,231,235].

Because of these conflicting results, and because some polymorphisms were associated with a better response, the DPWG did not consider that there were sufficient grounds to recommend a dose adjustment or a change of treatment in relation to *CYP1A2* polymorphism alone[215]. However, as previously mentioned, high plasma concentrations of olanzapine have been associated with clinically significant side effects such as sedation, orthostatic hypotension, tachycardia, seizures, anticholinergic side effects and cognitive impairment[203]. In addition, the combination of olanzapine with a potent CYP1A2 inhibitor (fluvoxamine) resulted in a prolongation of the QTc interval[203]. Therefore, it cannot be excluded that *CYP1A2*1A/*1A* or *CYP1A2*1A/*1F* patients taking a moderate or weak CYP1A2 inhibitor may have an olanzapine plasma concentration above the threshold for side effects. If the pharmacogenetic status of patients is not known, if plasma concentrations are not measured and if side effects are not systematically monitored using a scale, it is likely that these patients could experience a greater number of side effects and therefore poorer compliance with their treatment, without clinicians being aware of this, as moderate inhibitors do not normally cause clinically significant effects. Conversely, *CYP1A2*1F* has been associated with greater inducibility, for example by smoking[215,236], so not knowing the pharmacogenetic status does not allow to predict the impact of smoking on plasma concentration of olanzapine, which is of concern given that about 70% of patients with schizophrenia are smokers[206].

Looking at the two minor metabolizing pathways of olanzapine, one small study found a correlation between CYP2D6 activity and olanzapine plasma concentration (i.e. between PM and NM)[237], but all other studies found no association[220]. This is consistent with the minor role of CYPD6 in the olanzapine metabolism pathway[227,233], leading the DPWG to conclude that there is no gene-drug interaction between *CYP2D6* and olanzapine. As with

CYP2D6, all but one study found no association between *CYP3A* polymorphism and olanzapine exposure[238,239]. The only study to find an association also showed that CYP3A5 non-expressors have a higher risk of dry mouth, although this is the vast majority of the Caucasian population[239]. The DPWG therefore considered that there is no gene-drug association with CYP3A either[215].

- Aripiprazole

Aripiprazole is primarily metabolised to its active metabolite, dehydro-aripiprazole, by CYP2D6 and CYP3A4[82]. Conflicting results have been found regarding the impact of *CY3A4/5* polymorphism on aripiprazole plasma concentration[238], but high-quality data have established a link between CYP2A6 activity and aripiprazole exposure. Specifically, *CYP2D6* PM exhibit an increased concentration of aripiprazole[240]. Elevated plasma concentration of aripiprazole, as noted above, increase the incidence and severity of adverse events[219]. On this basis, the DPWG[215] and the U.S. Food and Drug Administration[238] recommend a maximum of 10 mg per day of the oral drug and a maximum of 300 mg per month of the long-acting injection in *CYP2D6* PM patients. However, a recent large cohort study of 1334 patients treated with aripiprazole found no impact of *CYP2D6* PM on the incidence of switching from aripiprazole to another antipsychotic, unlike risperidone[219]. This may be due to dose titration, as PM patients received a lower daily dose than NMs, or to under-reporting of adverse events by patients. Therefore, dose adjustment of aripiprazole in PM patients cannot be ruled out.

VARIANTS AFFECTING PHARMACODYNAMICS

- D_2 receptors

Dopamine D_2 receptors (DRD2) are the target of antipsychotics, responsible for their efficacy, and there is a correlation between the percentage of D_2 receptor occupancy and the reduction in psychotic symptoms[78,79]. For this reason, it has been suspected that a genetic polymorphism in the gene coding

for these receptors could have an impact on the binding of antipsychotics to these DRD2 receptors and therefore on the response to antipsychotics. Several studies have shown that the rs1799978 variant (carriers of -141C Del) is associated with a longer response time[241] and a poorer response to antipsychotics[242,243], with the strongest data concerning risperidone[244], although a large amount of data is also available for olanzapine. Many other variants have been reported to be associated with efficacy or side effects, but the data are too limited to draw any definitive conclusions.

Carriers of another variant, the T allele of rs2514218, showed a smaller reduction in positive symptoms than patients homozygous for the C allele. This variant was also associated with greater akathisia with aripiprazole and greater prolactin elevation with risperidone in men[245]. However, the impact of the *DRD2* polymorphism on the tolerability of antipsychotics is controversial, with conflicting results regarding risperidone-induced weight gain[246,247] and hyperprolactinaemia[247,248], although some variants are associated with greater weight gain with olanzapine[246,249].

No recommendation is currently available concerning the *DRD2* polymorphism because the level of evidence is considered to be too low.

- 5-HT_{2A} receptors

Impact of *5-HT_{2A} receptors* polymorphism on response to antipsychotics have also been tested and was found not to be associated with efficacy of risperidone[250,251] or olanzapine [234]. This is not surprising knowing that these receptors are not linked with antipsychotic efficacy. However, some polymorphisms (e.g. rs6313) were associated with better improvement of negative symptoms with risperidone[251] and with a better reduction of positive symptoms and anxiety with olanzapine although no significant impact on the total PANSS scores reduction were found. Regarding impact on side effects, data are inconsistent and very few are available, so as for *DRD2*.

- 5-HT_{2C} receptors

Unlike the previous receptors, there is an abundant literature on the impact of polymorphism of the gene coding for 5-HT2C receptors (HTR2C) on side effects of antipsychotics, and more specifically on weight gain and metabolic syndrome, as these receptors are known to be involved in appetite and food intake. The -759C/T promoter polymorphism (rs3813929) of the *HTR2C* gene has been associated with antipsychotic-induced weight gain, particularly in patients treated with olanzapine and clozapine, but also, to a lesser extent, with risperidone[252,253]. However, this polymorphism was not associated with metabolic syndrome in a more recent meta-analysis, whereas other variants (rs1414334) and the -697C allele (rs518147) were significantly associated with a greater risk of metabolic syndrome in schizophrenic patients[254].

- Other receptors

Many other variants have been tested for their potential association with adverse effects of antipsychotics, such as the melanocortin 4 receptor gene. Indeed, the rs489693 variant has been associated with the likelihood of hypertriglyceridemia and weight gain in schizophrenic patients treated with amisulpride, aripiprazole, clozapine, haloperidol, quetiapine, risperidone or ziprasidone[255], results which were reproduced in a naturalistic study[256].

Identifying genetic variants responsible for poor response or high side effect could lead to appropriate drug selection and/or drug dosing. This optimisation in the prescription of antipsychotics could lead to a better care and functioning of patients.

3.4. SUBSTANCE ABUSE

Around 40% of individuals with schizophrenia also have a comorbid non-alcoholic substance use disorder (SUD)[257] (excluding tobacco and caffeine), which is greatly superior to the prevalence observed in the general population in Belgium, estimated at 3.4%[258]. Moreover, the prevalence of

SUD is two to three times higher in men than in women[259], which is similar to what is found in the general population[259]. The main substances used in this population are cannabis followed by stimulants[259]. It has been shown, as mentioned above, that people who use cannabis have an earlier onset of schizophrenia at around 2.7 years, but they also have a higher risk of developing the illness[189]. Substance use, by inducing psychotic symptoms, can complicate the diagnosis at first presentation, as it can be difficult to know whether the symptoms are substance-induced or whether there is an underlying psychotic condition[189]. After the onset of schizophrenia, SUD complicates the clinical picture by contributing to a more complex clinical presentation[259]. Psychostimulants such as cocaine and amphetamines increase dopamine levels, thereby aggravating psychotic symptoms[27]. In addition, cannabis use strongly increases the risk of psychotic relapse[260], and patients with a dual diagnosis of schizophrenia and SUD are hospitalised two to three times more often in the long term than people with schizophrenia alone[261].

All types of SUD are strongly associated with a higher PANSS score for positive symptoms[262,263], and patients are also more likely to engage in violent behaviour[263,264] and 17-times more likely to commit homicides, compared to individuals with a diagnosis of schizophrenia alone[262]. Depressive symptoms are also more severe in these patients[262], as are suicidal ideation and suicide attempts, although this does not appear to increase the number of deaths by suicide in the end[261]. The effect of SUD on other symptoms of schizophrenia (i.e. negative and cognitive) is less clear[263]. Substance abuse also leads to unintentional poor treatment adherence due to impairment in patients' psychopathology that interferes with their ability to take their medication on a regular basis[194].

Alcohol use disorder affects about 20% of individuals with schizophrenia, which is again higher than the general population, estimated at around 10%[207,258]. However, effect of alcohol on psychotic symptoms is less clear, with some studies reporting more hallucinations and worsening of depressive symptoms[262] while others found no effect on psychotic symptoms when

alcohol is used alone[264]. Nevertheless, alcohol use disorder worsens the physical health and long-term outcomes of people with schizophrenia[189].

Patients with schizophrenia are also much more likely to smoke than the general population (OR= 5.9; 95% CI 4.9–5.7)[265]. As mentioned above, tobacco smoke acts as a pharmacokinetic inducer of the CYP1A2[82], lowering plasma concentration of antipsychotics metabolised by this pathway (i.e. clozapine and olanzapine), thereby increasing the risk of worsening psychotic symptoms[205]. In addition, smoking is responsible for most of premature deaths in people with schizophrenia[189]. Smoking cessation advice is given less frequently in individuals with a mental illness[266]. This is of concern because patients on antipsychotics should be warned against abrupt smoking cessation without medical support, as dosage adjustments are necessary for some drugs.

Finally, individuals with schizophrenia are heavier caffeine consumers than the general population and are also more likely to suffer from caffeinism. Although the European Food and Safety Authority considers consumption of less than 400 mg to be safe[267], the most widely accepted definition of caffeinism is consumption of more than 700 mg of caffeine a day[268-271]. The amount of caffeine contained in beverages varies considerably from region to region, but a cup of filter coffee is often considered to contain around 100 mg of caffeine[272]. High doses of caffeine cause anxiety, insomnia, agitation and irritability[272]. A worsening of hallucinations and delusions has been described in case reports in schizophrenic patients who had increased their daily caffeine intake[273-276], but the data are limited. As caffeine is contained in many products, actual daily consumption is difficult to monitor (Table 9).

Table 9. Average amount of caffeine in different types of food and drink in Europe.

Source of caffeine	Amount of caffeine
An espresso (60 mL)	80 mg
A cup of filter coffee (200 mL)	90 mg
A cup of black tea (220 mL)	50 mg
A standard can of cola (355 mL)	40 mg
A standard can of energy drink (250 mL)	80 mg
A bar of plain chocolate (50 g)	25 mg
A bar of milk chocolate (50 g)	10 mg

Figures are approximate and may vary within and across countries. Data from the European Food and Safety Authority[267]

In conclusion, because of the significant impact of substance use on outcomes in schizophrenia, patients with a dual diagnosis of schizophrenia and substance use should be carefully identified and monitored, and cessation advice and interventions should be encouraged.

3.5. GENDER

Gender differences in response to antipsychotics are attracting increasing attention. It is already known that schizophrenia affects slightly more men than women, with a ratio of 1.4:1, and that men tend to have an earlier onset of the disease, by an average of 3 to 4 years[277].

First, studies in the 80s and 90s suggested that women show faster and better improvement to typical antipsychotic, which was assumed to be due to the antidopaminergic effects of oestrogens as these effects seem to disappear after the menopause[278]. This is consistent with the peak incidence of schizophrenia in women in the perimenopausal period[277]. It may also explain the exacerbation of psychotic symptoms after childbirth, when oestrogen levels fall[279]. Studies have also shown a higher plasma concentration of antipsychotics in women than in men for the same dose [280], which is thought to be due to inhibition of certain CYP, such as CYP1A2, by oestrogens. Indeed, a multivariable analysis revealed that olanzapine plasma concentration was approximately 10% higher in women[281].

However, in a more recent multicentre study taking into account potential confounding factors, no difference was found between men and women in terms of symptom improvement on olanzapine, risperidone, clozapine and typical antipsychotics. The slight variation in plasma concentration thus does not appear to affect clinical efficacy. Two other studies of amisulpride and risperidone also found no gender differences in the efficacy of antipsychotics[282]. Only a better quality of life at 6 months was observed in women in an olanzapine cohort[278]. This result is consistent with other findings showing that women with schizophrenia are doing better in their daily lives, with more employment posthospitalisation, fewer troubles with the law and more relationships than men[280]. However, these better outcomes may have nothing to do with response. In fact, women are more adherent to antipsychotics and have a stronger therapeutic alliance as they are more likely to recognise the need for treatment[282], but they also have a different lifestyle and social support[280].

In addition, when comparing the efficacy of antipsychotics between men and women, it is important to take confounding factors into account. For example, some of the pharmacokinetic variations found in early studies were due to men being heavier smokers than women, which was confirmed by other studies that found no differences in antipsychotic doses between gender when smoking status was controlled[280]. Moreover, substance abuse is more prevalent in men, exposing them to a higher risk of poor response, while women tend to have more comorbidities, exposing them to a higher likelihood of drug-drug interactions[280]. Furthermore, as the age of onset and peak incidence differ between men and women, it is also important to consider age when comparing antipsychotic response between gender[280]. Finally, the effect of combined contraceptive pills on the pharmacokinetics of antipsychotics must also be considered. Co-administration of a contraceptive pill containing ethinylestradiol and levonorgestrel does not modify the efficacy or adverse effects of ziprasidone, an atypical antipsychotic metabolised by CYP3A4, as it has been shown that hormone replacement therapy or oral contraceptive do not influence CYP3A activity[280]. However, CYP1A2-mediated caffeine metabolism is inhibited by concomitant oestrogen replacement therapy[283]. This has led to trials of the use of oestrogenes as adjunctive therapy to antipsychotics, with positive results for oestradiol or ethinylestradiol alone on psychotic symptoms, although these were not replicated in a RCT of combined oral contraceptives where no significant benefit on antipsychotic efficacy was found[279,284].

In conclusion, as findings are still inconsistent, it is not possible to draw any definitive conclusions regarding the daily dose or the choice of antipsychotics according to gender, and the impact of gender on antipsychotic response.

3.6. REAL TREATMENT-RESISTANCE

Although about one third of individuals with schizophrenia are considered treatment-resistant (i.e. absence of sufficient response to two different antipsychotics), many are resistant for the reasons given above, such as cannabis use[285] or low plasma concentrations[192,193].

However, a number of patients may be resistant to treatment without any of the factors mentioned previously, and may qualify as real treatment resistant. It remains unclear whether these patients are suffering from a more severe form of schizophrenia or whether it is a distinct subtype of the disease[286].

Factors that support the existence of different subtypes are cognitive differences, with TRS patients performing less well in verbal learning and memory[286], but also differences in neuroimaging. Indeed, TRS patients have greater reduction of grey matter especially in the frontal cortex, increased volume of white matter, reduced striatal dopamine synthesis and a greater concentration of glutamate in certain areas of the cortex[286]. In addition, patients with TRS who respond to clozapine also have lower levels of dopamine in the putamen, and a low capacity of dopamine synthesis[286]. This may explain their response to clozapine, which is suspected to act not only on dopamine receptors[95,96] but also on NMDA glutamate receptors[33]. This is also consistent with findings that TRS patients are resistant even when more than 95% of D_2 receptors are occupied, but whether this is due to D_2 receptors polymorphism remains controversial[286]. Genetic studies using polygenic risk score analysis have attempted to find loci associated with TRS, using clozapine as a proxy, but the results are also contradictory[286,287].

As a result, real treatment resistance leads to low employment, poor occupational and social functioning, and patients with TRS generate costs 3 to 11 times higher than other patients with schizophrenia[288]. Patients with an early onset are much more likely to be treatment-resistant[289], as are patients with a longer duration of untreated psychosis[286]. TRS is also more likely to be of paranoid subtype, but no gender has been associated with TRS, unlike schizophrenia[286]. Finally, up to 60% of patients with TRS are also resistant to

clozapine, known as clozapine-resistant schizophrenia or ultra-resistant schizophrenia. The most widely accepted definition is the absence of an adequate response with a clozapine plasma concentration greater than 350 ng/mL for at least 8 weeks[290]. These patients are likely to have an even worse functioning than TRS patients[290].

In conclusion, several factors affect the response to antipsychotics (Figure 11), and these factors must be considered when prescribing antipsychotics to avoid unnecessary APP.

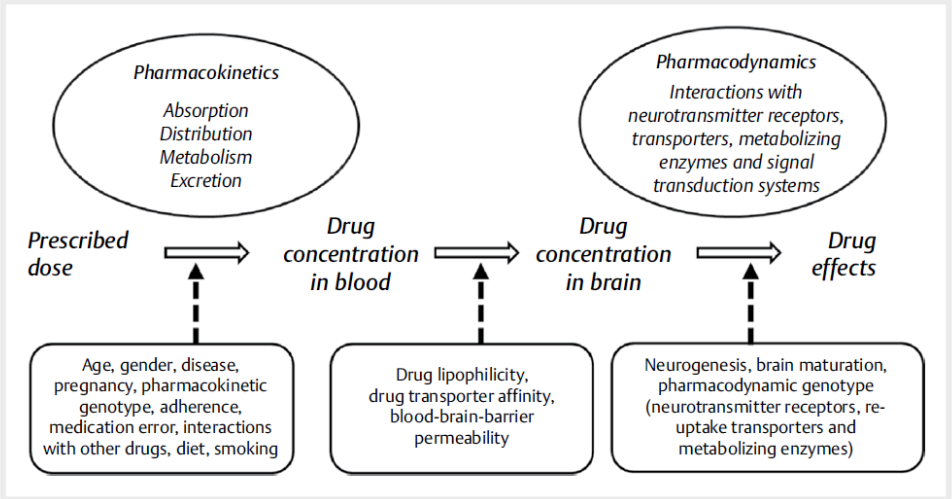

Figure 11. Factors affecting the drug effect. Extracted from Hiemke C. et al. (2018)[82]

4. FACTORS INFLUENCING PRESCRIBING BEHAVIOUR AND ADOPTION OF AN INNOVATION

In the past, clinicians relied on their own experiences to guide their prescribing behaviour, with perceived effectiveness guiding the choice of treatment[291]. However, in 1972, Archibald Cochrane published his book called 'Effectiveness and Efficiency: Random Reflections on Health Services', where he developed the concept of evidence-based medicine[292]. His ideas are based on the premise that clinicians' experience was prone to subjectivity, which could lead to substandard care. He argued that

randomised controlled trials allow to observe the objective, and therefore intrinsic, efficacy of a drug compared with a placebo[291]. The knowledge gained from these trials could then be disseminated by means of clinical guidelines or audits. The aim was to change the practice, with clinicians basing their prescribing decisions on the latest evidence applied to the individuality of each patient. However, tensions emerged between conservative views, arguing that this would lead to the loss of the privilege of autonomy, and a new vision of greater control over the day-to-day work of the practitioner to ensure that the best available treatment is prescribed[291].

Subsequently, it became apparent that, although a large proportion of clinicians have modified their behaviour on the basis of reports of rigorous trials conducted on patients, many still based their prescribing choices on perceived efficacy. This has led to greater attention being paid to the problem of implementing trial results into clinical practice[291].

Several barriers to the implementation of guidelines have been identified to date. A large review has shown that it affects knowledge, then attitude and finally behaviour[293]. Barriers related to knowledge are lack of awareness, that is being aware of the existence of a guideline, and lack of familiarity, which refers to knowledge of the content of a guideline[293]. These barriers may be due to lack of available time combined with the high volume of medical literature. Attitudinal barriers include lack of agreement with guidelines in general, for example in relation to autonomy of practice as mentioned above, and lack of agreement with a specific guideline, which could be due to a different interpretation of the evidence, a lack of confidence in a specific guideline or other influencing factors that will be described thereafter. Other attitudinal barriers include lack of self-efficacy, lack of outcome expectancy and inertia of practice. Lack of self-efficacy refers to believing that one cannot accomplish the behaviour and that only other clinicians can initiate it, and outcome expectancy refers to thinking that behaviour change will lead to the expected outcome. If a clinician does not believe that the recommendation will improve the outcome for the patient, they are unlikely to adopt the behaviour. In addition, inertia of practice appears to be a significant barrier, as it has been found in other studies that prescribing stability and continuity

were highly reported by physicians and that moments of change in prescribing behaviour were rarer[291]. Finally, knowledge and attitude are necessary but not sufficient to bring about a change in behaviour. Physicians may still come up against external barriers, such as the refusal of patients or their relatives to change, as well as environmental factors such as lack of resources or organisational constraints (Figure 12)[293]. Other external factors, such as the complexity of information, also constitute an obstacle to behavioural change. Indeed, simpler innovations spread faster, which affects people's knowledge, demonstrating the intertwined effect of knowledge, attitude and behaviour. Evidence synthesis may be a means of improving dissemination. Finally, the ability to test change also affects diffusion. Allowing a change in prescribing policy to be tested in a single hospital, for example, before being implementing across the whole country, would be one way of improving its uptake[294].

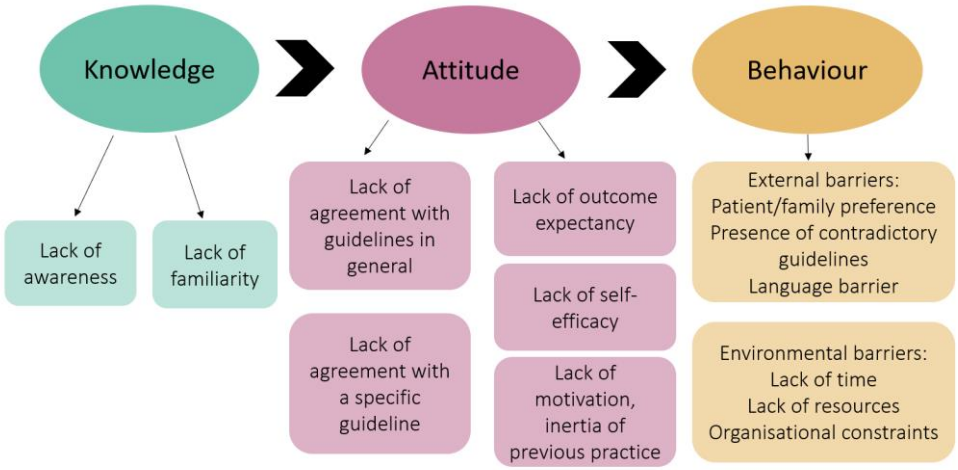

Figure 12. Sequence of barriers to physician adherence to clinical practice guidelines. Adapted from Cabana et al. (1999)

These barriers lead to the question of what can influence the knowledge, attitude and behaviour leading to rapid and even grateful diffusion and adoption of innovations, such as guidelines, which remains a challenge. It seems that the spread of innovation often relies on the interwoven combination of characteristics of the innovation[295], intrinsic characteristics of people[294], social contagion and social capital[296].

4.1. CHARACTERISTICS OF THE INNOVATION

People are more inclined to adopt innovations that provide more benefits or gains for them than risks. If the consequences are unknown or uncertain (i.e. lack of outcome expectancy), the status quo will persist to avoid the additional burden of change, especially for people who tend to avoid unfamiliar changes, leading to inertia of practice[294]. The observability of the result is also an important factor that can foster the adoption of the innovation by other physicians[294]. Indeed, it has been shown that guidelines for acute care are better followed than those for chronic illnesses[297]. The performance network effect, i.e. when the benefit of the innovation increases with the number of adopters[295], also plays an important role. The adoption of an innovation therefore depends on the characteristics of the innovation[295] and the personality and personal values of the adopter[294]. Added to this are external barriers such as the complexity of the innovation[297] or language barrier, which prevent clinicians from having a clear vision of the characteristics of the innovation, i.e. the benefits compared to the risks associated with adopting the innovation in the field of healthcare.

4.2. PHYSICIAN CHARACTERISTICS

A popular and widely validated classification of personal characteristics divides adopters into five categories: innovators, early adopters, early majority, late majority and laggards[294]. Innovators are described as being characterised by their adventurous spirit, tolerance of risk, fascination with novelty and willingness to leave their usual environment to learn. However, there are not opinion leaders, as they may be perceived as odd or reckless. Next come the early adopters, who are the opinion leaders because they are well integrated socially and do not invest as much as innovators in the search

for innovations. They are in contact with innovators, from whom they select the ideas they want to try, thanks to their resources and risk tolerance. As clinical leaders, they are often the target of pharmaceutical companies. The third group of individuals is the early majority, who observe the early adopters, further emphasising the importance of the observability of innovation outcomes for adoption, as discussed in the previous section. Their perspectives are more local than those of the first two groups, and they rely more on people they know well and personal familiarity than on science and theory before making a change. For example, physicians in this category would be more tempted to use innovations that meet their immediate needs than just interesting new ideas. The two last categories are the late majority and the laggards. The late majority observes the early majority and only adopts the innovation when it has become the new norm, i.e. when the majority of the population has adopted it, which is known as the standard of practice in medicine. Finally, the laggards, also called traditionalists, only make choices on the basis of their personal trials (Figure 13)[294].

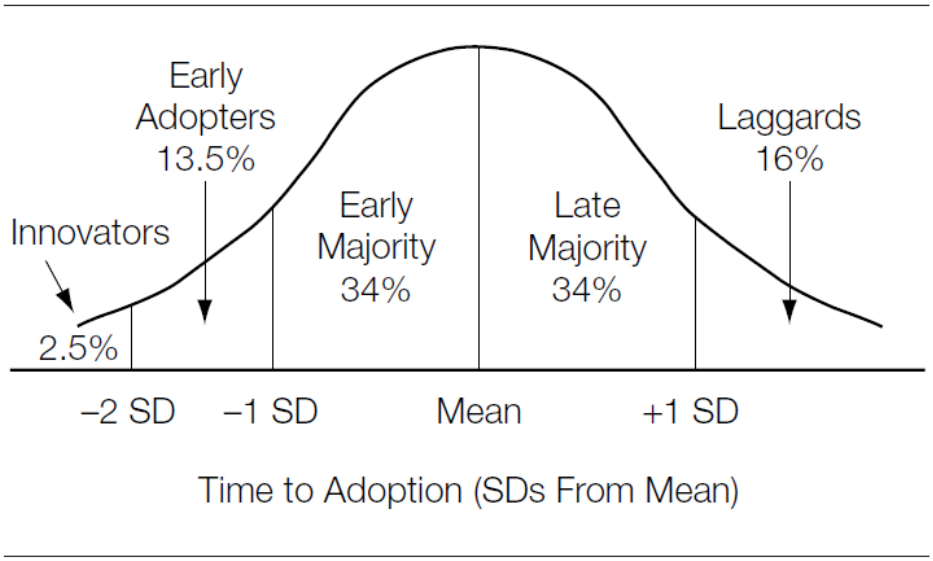

Figure 13. Adopter categorization of the basis of innovativeness. Extracted from Berwick, D.M. 2003

4.3. THE SOCIAL CONTAGION

In addition to intrinsic personality, the adoption of an innovation involves others aspects such as social contagion.

The diffusion leading to adoption is often driven by different means: information transfer, where a simple discussion can influence attitude and then behaviour, but also normative pressure and competitive pressure. Normative pressure is the dissonance and therefore discomfort that arises when valuable peers have adopted an innovation and one has not yet[295]. This behaviour can also be driven by the process of social comparison, where an individual compares their own behaviour with that of the reference group, especially when situations are ambiguous[298]. This would be particularly true for people in the "late majority". Conversely, competitive pressure can emerged when rivals have adopted the innovation and may obtain competitive advantage unless one adopt it as well[295].

All these innovations need social contacts to be disseminated, in addition to the factors expressed above (e.g. innovation characteristics, adopter personality). Social capital can be measured by different means. The first is called the "name generator". It involves mapping an ego-centred social network from person's response to identify the people with whom they talk about a specific topic. The network then extends from that person to a subsequent inventory of social resources (i.e. other people based on the inclusion of names). This method generates very detailed information about the network but is very burdensome, especially for large networks, and has some limitations. First, different questions may lead to different networks depending on their focus, due to the inclusion of different resources, leading to inconsistent findings. Second, redundancy can occur if the same resource is given by different individuals in the network. Third, a single resource is usually sufficient to solve a problem, and it is thus more useful to detect access to at least one resource than having to know the total amount of resources for each problem. Finally, most of these measures refer to social relationships rather than focusing on the resource available when needed. It is therefore not certain that these relationships constitute a reliable measure

for detecting access to resources[299]. Another method is the "position generator", which represents a set of resources based on job prestige or other position-related dimensions in a hierarchically modelled society (e.g. highest access prestige). However, little is known about the resource accessed and their proximity to the respondent. Furthermore, this method is less applicable in the professional domain of healthcare, as most resources have a similar hierarchical position[299]. A final method, called the Resource Generator, consists of a list of potential resources aimed at identifying the strength of the link through which a resource is accessed, in different life domains[299]. It is a combination of a name generator and a position generator. This method better reflects the support a person can access through their relationships, rather than the hypothetical assistance from known people measured by previous methods.

The role of social capital in the adoption of a medical innovation is the subject of debate. Although Collemann (1966) suggested that the more connected a person is (i.e. the larger their network), the more likely they are to adopt an innovation, other researchers have disputed this conclusion[298]. They argue that the adoption of the innovation tested in Colleman's study (i.e. an antibiotic) was due to marketing effort rather than simple diffusion among physicians. It appears that the structure of the network is more important than its size[298]. Denser networks, where people are highly interconnected, make it easier to disseminate the information they contain. However, as we saw above, this does not necessarily mean that individuals will adopt an innovation, which depends on a number of factors expressed previously. However, cohesive groups or cliques are very effective in exerting pressure to conform, through the effect of normative pressure.[298] This implies that any new information or innovation must first penetrate this dense network, which is the theory of structural holes. In a dense and highly cohesive network, information will circulate between colleagues and create redundancy, making it more difficult for new innovations to penetrate, as normative pressure generates resistance to new information from outside the network.[296]. Furthermore, because of the limited time available, physicians tend to socialise with each other's around shared opinions and values[300], creating an "echo", i.e. a network where the same information and

opinions circulate[296], hindering the possibility of accessing external and diverse clinical knowledge. This creates structural holes between networks that do not share the same opinions[296]. According to this theory, in countries where a certain prescribing behaviour is an established practice, higher social capital would have a positive effect on attitudes toward this behaviour[296]. As a corollary, in countries where the behaviour is still an innovation, it will be less likely to penetrate dense networks of highly cohesive physicians as it will be perceived as coming from outside the network, such as from the international scientific community[296].

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OBJECTIVES

Antipsychotic polypharmacy (APP), the simultaneous use of two or more antipsychotics by one patient, is common worldwide for the treatment of schizophrenia, despite that its greater efficacy over antipsychotic monotherapy is not supported by high-quality evidence. Worse, patients on APP experience poorer outcomes than those on antipsychotic monotherapy.

With the help of translational research and a multidisciplinary team, the aim of the present thesis is to provide insight about the ways of improving individual pharmacotherapy with antipsychotics in patients suffering from schizophrenia.

The aim of the first chapter is to explore the current situation in Belgium regarding the prescribing of APP and clozapine in schizophrenia, and to compare the prescribing and deprescribing practices of psychotropic drugs in hospitals between Belgium and Québec, with the aim of identifying opportunities for improvement and stimulating change.

The second chapter aims to detect the current attitude of psychiatrists towards APP in schizophrenia, as well as to understand what may influence their opinion. This would allow to identify specific situations where APP is still considered justified by the majority of psychiatrists and situations where it is unclear whether it is appropriate or not, in order to specifically address these situations in the future (e.g., during training sessions). The identification of factors influencing psychiatrists' opinions of APP (e.g. social capital, intrinsic evidence-based orientation) is intended to assist in the planning of future implementation studies. Moreover, the development of a scale measuring psychiatrists' social capital, in addition to being useful for the purpose of this chapter, will allow the scale to be used for other research questions requiring the measurement of psychiatrists' social capital.

Finally, the objective of the third chapter is to detect the factors affecting the response to antipsychotics, with the aim of providing personalised care for patients, not only regarding the prescription of psychotropic drugs, but also other environmental factors. Indeed, poor response often leads to APP, and understanding what leads to these situations (e.g. genetic polymorphism,

caffeine consumption) aims to propose changes in the future to improve the psychopathology of patients, and thus reduce the use of APP. In the first study of this chapter, we sought to detect the impact of caffeine withdrawal on the daily dose of antipsychotics and benzodiazepines and on patient functioning, as it is known that high caffeine consumption worsens the psychotic symptoms in schizophrenia. Caffeine consumption is part of the personalisation of patient treatment, which should not focus solely on prescribed medicines. The second study of Chapter III aims to detect genetic polymorphism in pharmacogenes that may be associated with antipsychotic plasma concentration and response, with a particular focus on olanzapine, which is the most frequently prescribed antipsychotic in Belgium. This study will also demonstrate the feasibility of measuring antipsychotic plasma concentrations and performing genetic tests in psychiatric hospitals, with the aim of implementing these tests in daily practice for targeted patients.

Together, the three chapters will provide insight of the different aspects that need to be considered to optimise the prescribing of antipsychotics in schizophrenia.

The specific objectives of each study are described in Table 1.

Table 1. Specific research objectives

Chapter	Specific objectives
I.1	To explore the evolution of antipsychotic polypharmacy and psychotropic prescribing patterns during a psychiatric hospitalisation To detect factors associated with antipsychotic polypharmacy To examine clozapine prescribing patterns
I.2	To determine factors associated with antipsychotic deprescribing after a psychiatric hospitalisation To compare psychotropic prescribing patterns on admission and at discharge in several Belgian hospitals and a Canadian hospital
II.1	To develop and validate a scale measuring the professional social capital of psychiatrists: the Resource Generator for Psychiatrists (RG-Psy)
II.2	To identify psychiatrists' attitude toward the use of antipsychotic polypharmacy in the treatment of schizophrenia To detect factors (e.g. social capital, demographics, intrinsic orientation toward EBM) associated with a more evidence-based attitude toward antipsychotic polypharmacy
III.1	To investigate the evolution of psychotropic prescribing patterns, and patient and hospitalisation characteristics following the withdrawal of caffeine availability within a hospital
III.2	To measure the correlation between plasma concentration of olanzapine and genetic polymorphism of a panel of pharmacogenes, considering co-factors (e.g. drug-drug interactions, smoking) To measure the correlation between clinical response, plasma concentration of olanzapine and genetic polymorphism

CHAPTER I
Prescribing and deprescribing of antipsychotics

CHAPTER I

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Antipsychotic polypharmacy and clozapine prescribing patterns: evolution and correlates before and after a psychiatric hospitalisation

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ABSTRACT

Aim: To explore the evolution of antipsychotic polypharmacy (APP) and other psychotropic prescribing patterns during psychiatric hospitalisations, to detect characteristics associated with APP on admission and at discharge, and to examine clozapine prescribing patterns.

Methods: Data on adult inpatients diagnosed with schizophrenia spectrum disorders were collected retrospectively from 6 Belgian hospitals.

Results: Of the 516 patients included, APP prescribing increased significantly from 47.9% on hospital admission to 59.1% at discharge. On admission and at discharge, APP was associated with prior clozapine use ($OR_{admission}$=2.53, CI=1.1-5.84, $OR_{discharge}$=11.01, CI=4.45-27.28), treatment with a first-generation antipsychotic ($OR_{admission}$=26.79, CI=13.08-54.86, $OR_{discharge}$=25.2, CI=12.2-52.04), increased antipsychotic exposure ($OR_{admission}$=8.93, CI=5.13-15.56, $OR_{discharge}$=19.89, CI=10-39.54), and a greater number of hypno-sedatives ($OR_{admission}$=1.88, CI=1.23-2.88, $OR_{discharge}$=4.18, CI=2.53-6.91). APP was negatively associated with involuntary admission ($OR_{admission}$=0.31, CI=0.14-0.7, $OR_{discharge}$=0.3, CI=0.13-0.68). When using an alternative definition of monotherapy (i.e., including patients with an add-on low-dose antipsychotic for sleep disorders), alcohol use disorder ($OR_{admission}$=0.26, CI=0.13-0.54) and higher age ($OR_{discharge}$=0.53, CI=0.29-0.95) were negatively associated with APP, and living in a residential facility ($OR_{discharge}$=2.39 CI=1.21-4.71) and a higher daily dosage of benzodiazepines during the stay ($OR_{discharge}$=1.32 CI=1.03-1.69) increased the odds of being discharged on APP. On admission, 9.3% of patients were being treated with clozapine. Although 28.1% of patients were eligible for clozapine treatment, only 11% of patients were discharged with a clozapine prescription. For 7 of the 10 patients with a new clozapine prescription, it was directly prescribed in combination with another antipsychotic, without a prior trial of clozapine monotherapy.

Conclusion: Suboptimal prescriptions of antipsychotics in patients with schizophrenia persist after psychiatric hospitalisations and are associated with identifiable characteristics.

INTRODUCTION

Antipsychotic polypharmacy (APP), defined as prescription of at least two different antipsychotics, is frequent worldwide in the treatment of schizophrenia [1]. Justifications given for APP use include attempting to reduce psychotic symptoms, targeting a comorbid condition (e.g., substance use disorder, anxiety), reducing adverse effects, and increasing adherence [2,3]. Despite these beliefs, high-quality evidence reveals that APP, excluding some combinations with clozapine, has no benefit over monotherapy on the reduction of positive or negative symptoms, or hospital readmissions [4-6]. Moreover, it is associated with a higher prevalence of adverse effects, increased healthcare costs, poorer treatment adherence, and increased risk of drug-drug interactions [7-10]. Some combinations are associated with an increased risk of hospital readmission [11]. International prescribing guidelines for schizophrenia thus advise against the use of APP, even for patients with psychiatric comorbidities [12-14].

About one third of individuals with schizophrenia will not respond sufficiently to treatment, with no or minimal symptom improvement after two or more antipsychotic trials at an adequate dose and duration, referred to as treatment-resistant schizophrenia (TRS). Clozapine is the first choice for TRS because of its superior effectiveness, but is underused in eligible patients worldwide [15,16]. Clozapine underuse might expose patients to greater risk of APP prescription. Both clozapine underuse and APP prescribing are considered inappropriate prescribing [12].

The majority of patients receiving APP can be safely switched to monotherapy without symptom worsening, especially when the combination involves clozapine or a long-acting injectable antipsychotic (LAI). Switching to monotherapy is also associated with reduction of side effects and improvement in attention and executive functions [17-19]. Psychiatric hospitalisations, during which patients are closely observed by healthcare professionals, may be suitable occasions to re-evaluate patient pharmacotherapy and possibly to switch to monotherapy.

Most of the existing studies on APP were conducted in ambulatory settings and/or are characterised by a cross-sectional design, thereby limiting the possibility to monitor any modification in drug regimens. Therefore, little information is available on the evolution of APP and clozapine prescribing patterns during psychiatric hospitalisations.

Determining the evolution of APP, clozapine, and other psychotropic prescribing patterns during psychiatric hospitalisations and identifying associated factors (e.g., demographics, disease severity, co-treatment) may help detect patients or situations at higher risk of APP prescriptions, enabling future interventions to optimise antipsychotic prescriptions at discharge.

The objectives of this study were therefore: (1) to explore the evolution of APP and other psychotropics prescribing patterns during a psychiatric hospitalisation; (2) to detect characteristics associated with APP on admission and at discharge; (3) to examine clozapine prescribing patterns.

METHODS

Setting and data sources

Retrospective data from six Belgian hospitals were analysed in 2020-2021. Potential factors associated with APP were extracted from patients' medical records and prescribing patterns from local prescription software. Patients treated with antipsychotics were identified using the Anatomical Therapeutic Chemical (ATC)-group N05A, with the exclusion of lithium (ATC N05AN01).

Study population

Records of all patients aged 18 to 64 years old discharged from psychiatric units after an acute hospitalisation (less than 1 year) between 1st November 2018 and 1st November 2019, who were receiving at least one antipsychotic on admission and had a diagnosis of schizophrenia or schizoaffective disorder (ICD-11 code 6A20 and 6A21 or DSM-5 295.xx) were analysed retrospectively. If a patient had more than one admission during the study period, only the last complete hospitalization was included.

Evolution of the use of APP and co-treatment

The prevalence of APP and associated factors on hospital admission and at discharge was explored. APP is defined as the prescription of at least two different antipsychotics. However, many patients receive a low-dose antipsychotic for sleep disorders (e.g., prothipendyl ≤80 mg, clotiapine ≤40 mg, levomepromazine ≤ 100 mg, quetiapine ≤50 mg) combined with an antipsychotic for the treatment of their psychotic symptoms, and this combination may not always be considered as a real APP. A sensitivity analysis was thus performed to evaluate the influence of this category of patients on the results using an alternative definition of monotherapy. In this alternative definition, patients were considered to be on monotherapy when they received two antipsychotics if one was prescribed at low-dose for sleep disorders. The prevalence of use of other psychotropic drugs (e.g., antidepressants, mood stabilizers, benzodiazepines, trazodone or sedating antihistamines) and anticholinergics was also examined. Anticholinergics, i.e., procyclidine, trihexyphenidyl and biperiden, are used for the treatment of extrapyramidal symptoms.

Variables potentially associated with APP

Different factors were considered for their potential association with APP, based on the literature [1,20,21]. These factors encompassed demographics, disease characteristics, comorbidities, hospitalisation characteristics, antipsychotic treatment and co-treatment. The list of factors tested is available in the online Supplementary material (eTable 1).

Exposure to antipsychotics was expressed as the ratio of the prescribed daily dose (PDD) to the World Health Organization (WHO) approved defined daily dose (DDD). When patients were receiving more than one antipsychotic, the PDD/DDD ratio was calculated using the sum of PDD/DDD ratios for each prescribed antipsychotic.

The daily dose of benzodiazepines was calculated using a lorazepam equivalent dose based on the Belgian official compendium (CBIP/BCFI).

Hypno-sedative drugs used for the treatment of sleep disorders comprised low-dose antipsychotics, trazodone ≤100 mg, benzodiazepines, and sedating antihistamines, if they were taken at night to induce sleep.

The Global Assessment Functioning (GAF) score was used to estimate the severity of the patients' psychopathology. In Belgium, a GAF score is systematically determined on admission and at discharge for every patient hospitalised in a psychiatric unit.

Certain continuous variables were dichotomised (e.g., ≥2 or < 2 admissions in the year prior to the current hospitalisation and ≥2 or < 2 previous trials of an antipsychotic) to enable easier interpretation, based on different regression models.

Residential facilities referred to group homes, nursing homes, or supervised residential facilities for individuals with mental disorders.

Clozapine prescribing patterns

Clozapine prescribing patterns on admission and at discharge were also investigated. A patient was considered eligible for clozapine if they had an inadequate response to at least two different antipsychotic trials at a minimal dose of 400 mg of chlorpromazine equivalent, for at least 6 weeks [22]. Clozapine antipsychotic polypharmacy (CAP) was defined as the combination of clozapine with at least one other antipsychotic.

Statistical analysis

Changes in the prevalence of APP, psychotropic and anticholinergic prescribing between admission and discharge were measured using McNemar tests. Change in antipsychotic exposure was tested using a paired-sample Wilcoxon test.

A logistic regression model was used to detect factors associated with APP on admission and at discharge, with multiple imputation for missing data. A backward stepwise elimination based on the Akaike information criterion was used to select the final model, in which p-values <0.05 were considered

statistically significant. Changes in the prevalence of clozapine use, CAP, and other clozapine prescribing patterns between admission and discharge were examined using McNemar tests. The statistical analyses were performed using R software.

Ethics

The study protocol was approved by the Comité d'éthique hospitalo-facultaire Saint-Luc-UCLouvain (Belgium), as well as by ethics committee of each involved hospital (N°2019/27NOV/530).

RESULTS

Baseline characteristics

Of the 516 patients with schizophrenia or schizoaffective disorder hospitalised between 1st November 2018 and 1st November 2019, 55.4% were men and the mean age was 40 (±11.3) years. The majority of the patients admitted were unemployed (94.8%), 20.3% lived in a residential facility, and 42.3% had a legal guardian. The mean duration of hospitalisation was 27 days, and 20.2% of the patients were involuntary admissions (Table 1).

Table 1. Baseline characteristics

Characteristics	Total (N=516) n, (%)
Sociodemographic characteristics	
Male	286 (55.4)
Female	230 (44.6)
Age (y), mean (SD)	40 (11.6)
Single	420 (81.4)
Living situation	
Residential facility	105 (20.3)
Homeless	48 (9.3)
Living alone or with relatives	363 (70.4)
Legal guardian	217 (42.3)
Unemployed	489 (94.8)
Medical characteristics	
Tobacco smoking	348 (67.6)
Alcohol use disorder	118 (22.9)
Substance use disorder	183 (35.6)
History of violent or aggressive behaviour	224 (43.6)
Intellectual disability	49 (9.5)
Prior suicide attempt	135 (26.6)
Illness duration (y), median (IQR)	12 (6-20)
Age of onset (y), median (IQR)	24 (19-30)
Hospitalisation characteristics	
Involuntary admission	104 (20.2)
Length of hospital stay (d), median (IQR)	27 (13-52)
GAF score on admission, mean (SD)	37 (13)
GAF score at discharge, mean (SD)	51 (16)
Antipsychotic adverse effect(s)	238 (46.2)
Primary diagnosis	
Schizophrenia	398 (77.1)
Schizoaffective disorder	118 (22.9)

Abbreviations: SD, standard deviation; IDR, Interquartile range

Evolution of antipsychotics and psychotropic prescribing patterns between admission and discharge

The prevalence of APP prescribing increased significantly from 47.9% on hospital admission to 59.1% at discharge (p<0.001) (Figure 1-A). At discharge, the daily number of antipsychotics had increased in 117 patients (22.7%), decreased in 48 patients (9.3%), and was unchanged in 351 patients (68%), compared to the situation on hospital admission. Although the daily number of antipsychotics decreased in 48 patients between admission and discharge, only 34 of the 247 patients (13.8%) admitted on APP were discharged on monotherapy (Figure 2). Antipsychotic exposure per patient increased significantly from 1.5 (IQR 1-2.3) to 1.8 (IQR 1.1-2.5) (p<0.001) between hospital admission and discharge. Using the alternative definition of monotherapy, APP was present in 35.5% (n=183) of patients on admission versus 44% (n=227) at discharge (p<0.001) (Figure 1-A). Of the 247 patients admitted on APP, 99 (40.1%) had a combination involving at least one LAI, and this figure increased to 145 of the 305 patients on APP (47.5%) at discharge (p<0.001). Paliperidone was the LAI antipsychotic most frequently prescribed to patients on APP, both on admission and at discharge (eTable 2 in Supplementary material). The proportion of patients taking mood stabilizers (16.9% versus 19.6%, p=0.008), benzodiazepines (45.5% versus 54.3%, p<0.001), anticholinergics (9.3% versus 11.6%, p=0.025), or low-dose antipsychotics for sleep disorders (22.1% versus 29.3%, p<0.001) increased significantly from admission to discharge, but there was no significant change in the prevalence of patients taking antidepressants (30.6% versus 33.1%, p=0.074) and trazodone or sedating antihistamines (12.8% versus 13.6%, p=0.635) (Figure 1-B).

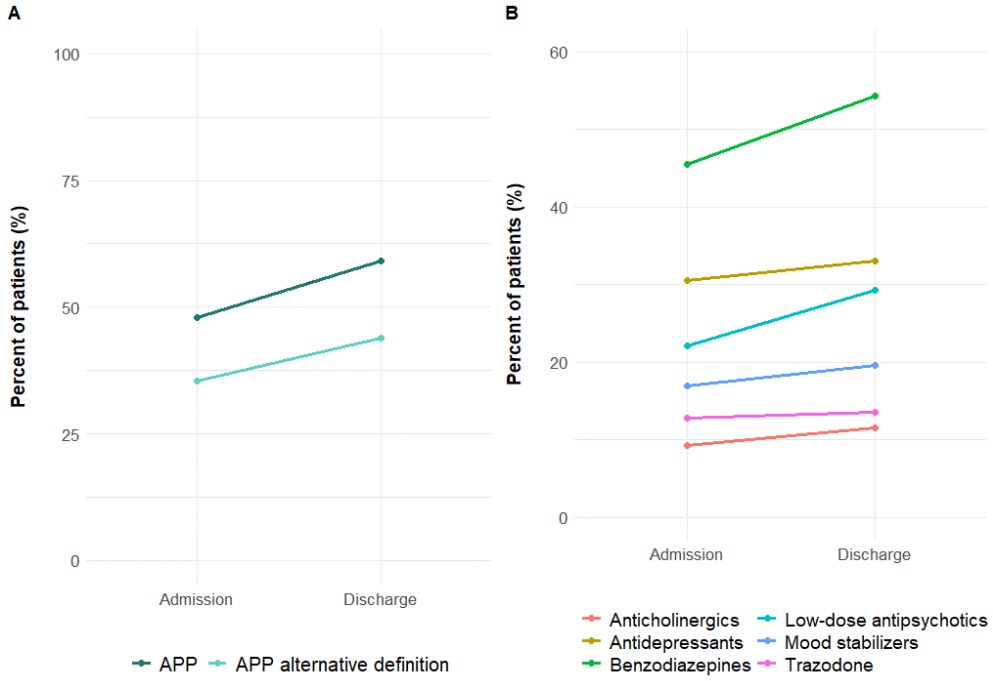

Figure 1

A. Evolution of the prevalence of antipsychotic polypharmacy prescribing between admission and discharge of psychiatric hospitalisations, with both definitions of monotherapy (N=516). There was a significant increase in the prevalence of APP after the psychiatric hospitalisations, independent of the definition used. APP, Antipsychotic polypharmacy; APP alternative definition, Antipsychotic polypharmacy with the alternative definition of monotherapy (i.e. including patients with one antipsychotic at a therapeutic dosage and one low-dose antipsychotic for the treatment of sleep disorders).

B. Evolution of the prevalence of psychotropics and anticholinergics between hospital admission and discharge (N=516). Prescriptions of benzodiazepines, mood stabilizers, anticholinergics and low-dose antipsychotics increased significantly after the hospital stay. There was no significant change in the prevalence of antidepressants or trazodone.

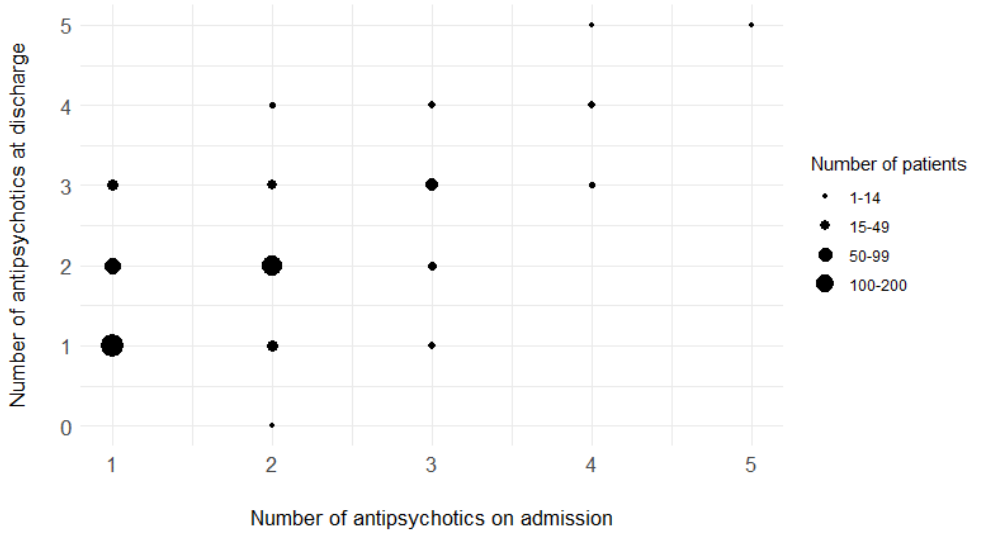

Figure 2. Number of antipsychotics per patient on hospital admission and at discharge.
Among patients admitted on antipsychotic monotherapy, 177 patients were discharged on monotherapy, 71 patients on two and 21 patients on three antipsychotics. Among patients admitted on two antipsychotics, 29 patients were discharged on monotherapy, 133 patients on two, 17 patients on three, and two patients on four antipsychotics. Among patients admitted on three antipsychotics, four patients were discharged on monotherapy, 12 patients on two, 36 patients on three, and five patients on four antipsychotics. Among patients admitted on four antipsychotics, two patients were discharged on three, four patients on four and one patient on five antipsychotics. One patient was admitted and discharged on 5 different antipsychotics.

Antipsychotic polypharmacy on hospital admission and associated factors

Among the 247 patients with APP on admission, 73.7% (n=182) were receiving two, 23.1% (n=57) three, and 3.2% (n=8) four or more different antipsychotics.

APP on hospital admission was significantly associated with a previous trial of two or more different antipsychotics (OR=5.1, 95% CI=1.95-13.33), prior

clozapine use (OR=2.53, 95% CI=1.1-5.84), treatment with a first-generation antipsychotic (FGA) (OR=26.79, 95% CI=13.08-54.86), higher exposure to antipsychotics (OR=8.93, 95% CI=5.13-15.56), and a greater number of hypno-sedative drugs (OR=1.88, 95% CI=1.23-2.88). Involuntary admission (OR=0.31 95% CI=0.14-0.7) was negatively associated with APP on admission (Table 2).

Table 2. Factors associated with antipsychotic polypharmacy on psychiatric hospital admission in the multivariable analysis

Variables	OR [CI 95%]	P-value
Patients characteristics		
Alcohol use disorder	0.57 [0.28-1.15]	0.117
Antipsychotic treatment		
At least one FGA	26.79 [13.08-54.86]	**<0.001**
At least 2 antipsychotic's trials	5.1 [1.95-13.33]	**<0.001**
Prior clozapine use	2.53 [1.1-5.84]	**0.03**
Antipsychotic's adverse effect(s)	1.54 [0.86-2.74]	0.146
PDD/DDD ratio on admission	8.93 [5.13-15.56]	**<0.001**
Hospitalisation		
Involuntary admission	0.31 [0.14-0.7]	**0.005**
Psychiatric hospital	2.04 [0.98-4.25]	0.058
Cotreatment		
Number of hypno-sedatives	1.88 [1.23-2.88]	**0.004**

FGA : First Generation Antipsychotic(s); PDD : Prescribed Daily Dose; DDD= Defined Daily Dose. p-values <0.05 are considered significant.

Low-dose antipsychotics for the treatment of insomnia were prescribed to 22.1% of patients (n=114) on admission. Using the alternative definition of monotherapy, 35.5% (n=183) of patients had APP on admission. In the sensitivity analysis using the new definition for APP, the same characteristics were associated with APP, except for involuntary admission. Treatment with

an antidepressant (OR=1.93 95% CI=1.07-3.46) or with trazodone or a sedating antihistamine (OR=4.29 95% CI=1.71-10.76) and not having an alcohol use disorder (AUD) (OR=0.26, CI=0.13-0.74) were also significantly associated with APP on admission (Table 3).

Table 3. Factors associated with antipsychotic polypharmacy on psychiatric hospital admission in the multivariable analysis using the alternative definition of monotherapy

Variables	OR [CI 95%]	P-value
Patients characteristics		
Alcohol use disorder	0.26 [0.13-0.54]	**<0.001**
Intellectual disability	2.4 [0.98-5.87]	0.056
At least 2 prior admissions in the year	1.6 [0.91-2.81]	0.102
Antipsychotic treatment		
At least one FGA	5.02 [2.68-9.38]	**<0.001**
At least 2 antipsychotic's trials	5.95 [2.01-17.59]	**0.001**
Prior clozapine use	2.27 [1.04-4.97]	**0.04**
PDD/DDD ratio on admission	10.76 [6.5-17.8]	**<0.001**
Hospitalisation		
Involuntary admission	0.51 [0.24-1.1]	0.085
Psychiatric hospital	1.84 [0.96-3.56]	0.067
Cotreatment		
Antidepressant	1.93 [1.07-3.46]	**0.029**
Trazodone or sedating antihistamine	4.29 [1.71-10.76]	**0.002**
Number of hypno-sedatives	0.44 [0.29-0.68]	**<0.001**

FGA : First Generation Antipsychotic(s); PDD : Prescribed Daily Dose; DDD= Defined Daily Dose. p-values <0.05, in bold, are considered significant.

APP at hospital discharge and associated factors

The same characteristics were associated with APP at hospital discharge as at hospital admission, except for the "previous trial of at least 2 different antipsychotics". In addition, APP at discharge was negatively associated with

treatment with trazodone or a sedating antihistamine (OR=0.32 95% CI=0.13-0.80) (Table 4).

Table 4. Factors associated with antipsychotic polypharmacy at hospital discharge in the multivariable analysis

Variables	OR [CI 95%]	P-value
Antipsychotic treatment		
At least one FGA	25.2 [12.20-52.04]	**<0.001**
Prior clozapine use	11.01 [4.45-27.28]	**<0.001**
PDD/DDD ratio at discharge	19.89 [10-39.54]	**<0.001**
Hospitalisation		
Involuntary admission	0.3 [0.13-0.68]	**0.004**
Cotreatment		
Trazodone or sedating antihistamine	0.32 [0.13-0.80]	**0.015**
Number of hypno-sedatives	4.18 [2.53-6.91]	**<0.001**

FGA : First Generation Antipsychotic(s); PDD : Prescribed Daily Dose; DDD: Defined Daily Dose. p-values <0.05, in bold, are considered significant.

Using the alternative definition of monotherapy, 44% (n=227) of the patients were discharged on APP. In this sensitivity analysis, similar characteristics were associated with APP at discharge, with the addition of lower age (OR=0.53, CI=0.29-0.95), living in a residential facility (OR=2.39, 95% CI=1.21-4.71), and a higher intake of benzodiazepines per day during the hospitalisation (OR=1.32 95% CI=1.03-1.69) (Table 5).

Table 5. Factors associated with antipsychotic polypharmacy at hospital discharge in the multivariable analysis using the alternative definition of monotherapy

Variables	OR [CI 95%]	P-value
Patients characteristics		
Age	0.53 [0.29-0.95]	**0.032**
Residential facility	2.39 [1.21-4.71]	**0.012**
Legal guardian	1.66 [0.95-2.9]	0.075
Age of onset	1.4 [0.95-2.07]	0.088
Antipsychotic treatment		
At least one FGA	3.93 [2.25-6.89]	**<0.001**
Prior clozapine use	4.05 [1.82-9]	**<0.001**
Antipsychotic's adverse effects	1.64 [0.99-2.71]	0.056
PDD/DDD ratio at discharge	15.36 [8.97-26.31]	**<0.001**
Hospitalisation		
Involuntary admission	0.38 [0.19-0.75]	**0.005**
Cotreatment		
Trazodone or sedating antihistamine(s)	2.21 [1.02-4.79]	**0.046**
Number of hypno-sedatives	0.67 [0.47-0.97]	**0.032**
Daily dose of benzodiazepine(s)[a]	1.32 [1.03-1.69]	**0.03**

FGA : First Generation Antipsychotic(s); PDD : Prescribed Daily Dose; DDD: Defined Daily Dose. p-values <0.05 are considered significant.

[a]Referred to as daily dose of benzodiazepines administered during the hospital stay

Clozapine prescribing patterns

Of the 516 patients analysed, 48 (9.3%) were being treated with clozapine on admission, the majority (n=34, 70.8%) as part of CAP. The antipsychotics most frequently combined with clozapine on admission were paliperidone (n=12) and aripiprazole (n=8). Clozapine was combined with a LAI in 15 of the 34 patients on CAP on admission

Although 145 patients (28.1%) were identified as eligible for clozapine therapy, it was introduced in only 10 patients during the hospitalisation, one of whom was not eligible and two had missing information on clozapine eligibility (eTable 3 in Supplementary material). In one patient who was

receiving clozapine on admission, it was deprescribed despite the patient being eligible for clozapine treatment; 57 (11%) patients were therefore discharged on clozapine, a significant increase compared to admission (p=0.016).

Significantly more patients discharged on clozapine were prescribed CAP compared to at hospital admission (n=34 versus n=43 respectively, p=0.016), and the CAP more often involved a combination with a LAI (n=15 versus n=21 respectively, p=0.041). In the majority of patients on CAP, the regimen involved one antipsychotic combined with clozapine, but there was a significant increase in the number of patients with CAP that included at least three different antipsychotics, from 6 patients on admission to 12 at discharge (p=0.041). Of the 10 patients in whom clozapine was started during the hospitalisation, 7 were started directly on CAP without a prior trial of clozapine monotherapy (eTable 3 in Supplementary material).

DISCUSSION

Almost half of our population on admission and about 60% of the patients at discharge were treated with APP, which is considerably higher than the average 23% prevalence of APP in Europe [1]. APP was also more widely prescribed in the current study compared to the Belgian situation 20 years ago (42.2% of all patients), confirming recent observations of a trend to increased APP prescribing [23]. This large difference from the European prevalence could in part be explained by the large use of low-dose antipsychotics for the treatment of sleep disorders in our population (n=151; 22.1%), which was considerably greater than the use of trazodone or sedating antihistamines (n=66; 12.8%). Indeed, sedating antihistamines are rarely used for insomnia in Belgium because they are not reimbursed by the national health insurance, whereas low-dose antipsychotics are. The use of low-dose antipsychotics for sleep disorders is controversial because of their risk of inducing daytime somnolence and worsening sleep-disordered breathing and sleepwalking [24]. Nevertheless, this trend has also been reported in other European countries where antipsychotics are increasingly

used at a low dosage for indications other than psychosis, and is therefore unlikely to fully explain the difference between our results and the European average [25]. When the alternative definition of monotherapy was used to detect what is sometimes considered as real APP, 35.5% of patients were still classified as receiving APP on admission. In addition, APP prescribing increased between admission and discharge, independent of the definition of monotherapy used. Among patients admitted on APP, only 19.5% had a decrease in the number of prescribed antipsychotics per day and only 13.8% were discharged on monotherapy. This observation highlights that psychiatric hospital stays are not sufficiently used to deprescribe or re-evaluate the relevance of certain inappropriate prescribing patterns. In acute episodes (e.g., in patients recently admitted to hospital), a higher daily dosage of antipsychotics may be temporarily necessary, and it is recommended to choose an antipsychotic with sedating properties or to add a short-term benzodiazepine when symptoms are very disturbing. Nonetheless, combining several antipsychotics is not recommended [12]. Thus, hospitalisations could be considered appropriate moments for deprescribing, because healthcare professionals can closely monitor the patients, and successful hospital-based deprescribing programs for antipsychotics have been described [26,27].

Prior use of clozapine and having already tried at least two different antipsychotics increased the risk of being prescribed APP. These findings suggest that TRS or subjective TRS (i.e., no or poor response to two antipsychotic trials even when sufficient dosage or duration is not reached) increases the odds of having APP. In addition, when using the alternative definition of monotherapy, patients living in residential facilities are more at risk of being discharged on APP. These patients are not able to live on their own, because their symptoms are too severe. However, more severe GAF scores were not correlated with APP in our sample. This score is mandatory in Belgium for every psychiatric hospitalisation, and is often considered a burden for clinicians. It is likely that it does not completely represent the psychopathological state of patients. Moreover, this score was part of the DSM-IV but is no longer used in the fifth version of the DSM of the American

Psychiatric Association because of poor reliability. Finally, involuntary admission was protective against APP. Patients admitted involuntarily are, by definition, patients who refuse any treatment; they are often anosognosic (i.e., not aware of their disease), and hence generally reluctant to take their medicines. Thus, it can be hypothesised from our data that severely ill patients still willing to be hospitalised are at increased risk of APP, whereas reluctance to be hospitalised may translate into reluctance to receive psychiatric care in general, making such patients less likely to receive APP.

Treatment with a FGA was highly correlated with the odds of APP at any point during the hospitalisation. It has been previously assumed that this effect was induced by the high utilisation of add-on low-dose antipsychotics for indications other than psychosis (e.g., sleep disorders, anxiety), because these antipsychotics are predominantly FGAs in Europe [1]. However, FGA use was still strongly associated with APP when using the larger definition of monotherapy, excluding this theory. Our data shows that the odds of APP were higher in patients with more severe disease, leading to the assumption that add-on FGAs are used for patients with poor treatment response as an attempt to further control symptoms. This finding is consistent with the previously reported justifications for APP [2,3,28]. In fact, the different pharmacological profile between FGAs and second-generation antipsychotics (SGAs) might furnish the belief that combining a FGA with a SGA leads to greater efficacy, despite not being supported by the literature [29].

Similar to prior data, APP increased the risk of receiving a higher daily dose of antipsychotics [20,21].

Having an AUD significantly reduced the probability of APP on admission when using the alternative definition of monotherapy, and remained in the model, although not reaching significance, with the stricter definition of monotherapy. The reasons underlying this finding remain unclear. The sedative and anxiolytic properties of alcohol might protect these patients from receiving an add-on low-dose antipsychotic for sedation or anxiety. However, as the effect of AUD was only significant when using the alternative

definition of monotherapy, its effects were only protective against what is sometimes referred to as real APP. Thus, this protection against APP is perhaps induced by the fear of increased adverse effects in the AUD population. AUD increases the risk of obstructive sleep apnoea, which is already a frequent comorbidity in patients with schizophrenia and can be worsened by APP [13].

At discharge, increased age reduced the odds of APP prescribing when using the alternative definition of monotherapy. Similar to the situation with AUD, prescribers might be more cautious with older patients who are more susceptible to adverse effects and thus avoid APP.

A higher daily benzodiazepine dose during the hospital stay significantly increased the probability of being discharged on APP when the alternative definition of monotherapy was used. High benzodiazepine use might indicate anxiety, agitation, or insomnia during the stay. Yet, APP at any time was associated with an increased number of hypno-sedative drugs and/or with trazodone depending on the definition of monotherapy used, translating a greater likelihood of being treated with APP when having sleep disorders. APP on admission was also associated with antidepressant prescriptions, but not with a diagnosis of schizoaffective disorder. Together, this suggests that APP is often motivated by an attempt to treat comorbid mental health conditions, such as anxiety, depression, or sleep disorders. However, these comorbidities should be appropriately treated rather than having recourse to APP, especially as it is proven that APP does not reduce depressive symptoms compared to antipsychotic monotherapy [4].

Despite being associated with APP in previous trials, having an antipsychotic adverse effect was not significantly associated with APP in our population, although it remained in the final regression model [7,9]. This may be explained by an under-detection of adverse effects, as rating scales for adverse effects are not systematically used in routine clinical practice.

Although about one third of patients were identified as being eligible for clozapine, which is consistent with the literature, only 11% were discharged

on clozapine. The majority of patients treated with clozapine on admission (70.8%) and at discharge (75.44%) were on CAP, although this regimen should be reserved for patients who are resistant to clozapine, estimated at around one third [22]. It has been shown that most patients can be safely switched to monotherapy without symptom worsening, especially when the combination involves clozapine [17]. Unfortunately, most patients who had clozapine introduced during the hospitalisation were directly prescribed CAP, without a prior trial of clozapine monotherapy. Moreover, less than one quarter of all patients on CAP received a combination of clozapine with aripiprazole on admission or at discharge, despite the fact that this is the only CAP with evidence of a greater efficacy than clozapine monotherapy [5]. In almost half of the patients on CAP, the combination was with an LAI, perhaps to ensure some cover for patients in the event of poor adherence to clozapine. However, as clozapine is reserved for TRS patients, they will not be protected against symptom worsening by the LAI in case of clozapine self-discontinuation. Another hypothesis could be that the psychiatrist was testing both lack of adherence and the presence of real TRS. However, poor adherence should be excluded in case of insufficient response by measuring the antipsychotic plasma concentration or by using a LAI to avoid using clozapine to patients who do not have real TRS [12]. Finally, although a minority, six of the patients on CAP on admission were receiving at least three antipsychotics and this number increased significantly to 12 at discharge. These observations indicate that ultra-resistant patients are more exposed to poor quality prescribing because of the difficulty in rationalising prescriptions in the face of non-response.

It has been proven that adherence to schizophrenia prescribing guidelines is associated with decreased costs and increased quality-adjusted life-years, so strategies to improve prescribing patterns should be encouraged [30].

Our data should be interpreted within their limitations. Cofactors were extracted from patients' medical records. In routine clinical practice, patients are not systematically assessed for antipsychotic adverse effects using rating scales, reducing the robustness of detection. It has been shown that patients

tend to underreport adverse effects, especially those considered embarrassing (e.g., sexual dysfunction, urinary incontinence) [31]. The admission history and numbers of previous antipsychotic trials were also identified through chart review, and might have been underestimated. However, these variables were dichotomised to increase accuracy. Finally, our study focused on prescribing patterns during a psychiatric hospitalisation, and some prescriptions may have been rapidly modified after discharge.

Our trial concerns prescribing patterns in six Belgian hospitals, and enables us to accurately reflect the Belgian situation. By reviewing medical records, we had more precise information than that extractable from our national database, where no information on daily dosage or use of as-needed drugs is available. This design also enabled detection of real polypharmacy, by excluding situations of switch. In addition, it is the first study to examine the evolution of antipsychotic prescribing patterns during psychiatric hospitalisations outside specific programs aiming at deprescribing. Our results provide a better understanding of the evolution of prescribing in patients with schizophrenia during a hospital stay and may support the development of targeted hospital-based interventions in the future.

In conclusion, suboptimal prescription of antipsychotics for patients with schizophrenia persists and the risk of occurrence is associated with identifiable characteristics. Psychiatric hospitalisations do not lead to treatment optimisation and studies assessing interventions to optimise antipsychotic use are needed. Clinical pharmacy services may support psychiatrists in the management of psychotropic medications.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

CONSENT TO PARTICIPATE

The requirement for informed consent to participate has been waived by the Ethics Committee.

ETHICS APPROVAL

The study protocol was approved by the Comité d'éthique hospitalo-facultaire Saint-Luc-UCLouvain (Belgium), as well as by ethics committee of each involved hospital (N°2019/27NOV/530).

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DATA AVAILABILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

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APPENDIX

eTable 1. List of factors tested for their potential association with antipsychotic polypharmacy

Demographics
Age
Sex
Relationship situation: single or in a relationship
Living situation: homeless, alone or with relatives, residential facility
Legal guardian/conservatorship
Employment
Comorbidities
Tobacco smoking
Alcohol use disorder
Substance use disorder (except alcohol)
Intellectual disability
Number of comorbidities
Characteristics of disease
Diagnosis: schizophrenia or schizoaffective disorder
Duration of illness
Age of illness onset
Prior suicide attempt(s)
2 or more previous admissions in the year prior to the current hospital stay
GAF score
Having a history or current violent or aggressive behaviour
Hospitalisation characteristics
Length of hospital stay
Involuntary admission
Hospital: psychiatric or general hospital
Prescriber status: senior or resident[a]
Antipsychotic treatment
Having at least one long-acting injectable antipsychotic
Having at least one first-generation antipsychotic
Antipsychotic exposure (i.e. PDD/DDD ratio)
2 or more previous trials of different antipsychotics
Prior use of clozapine
Clozapine eligibility
Experiencing an antipsychotics' side effect
Administration of an "as needed" antipsychotic during the hospital stay[a]
Cotreatment
Antidepressant
Mood stabilizer (i.e. lithium, valproate, lamotrigine)
Benzodiazepine
Trazodone or sedating antihistamine
Number of psychotropics cotreatment
Number of hypno-sedative drugs
Anticholinergics
Anticholinergics administered during the hospital stay[a]
Daily dose of benzodiazepines received during the hospital stay[a]

[a]Factors only tested at discharge

GAF; Global Assessment Functioning score, PDD; Prescribed Daily Dose, DDD; Defined Daily Dose

eTable 2. Prevalence of each long-acting injectable antipsychotic prescribed to patients on APP

LAI antipsychotics involved in APP	Admission Total (N=99)[a] n, (%)	Discharge Total (N=145)[a] n, (%)
Aripiprazole LAI	16 (16.2)	27 (18.6)
Bromperidol LAI[b]	1 (1.1)	0 (0)
Flupentixol LAI	1 (1.1)	1 (0.7)
Haloperidol LAI	7 (7.1)	9 (6.2)
Olanzapine LAI	10 (10.1)	13 (9)
Paliperidone LAI (every month)	46 (46.5)	75 (51.7)
Paliperidone LAI (every 3 months)	7 (7.1)	13 (9)
Risperidone LAI	8 (8.1)	8 (5.5)
Zuclopenthixol LAI (decanoate)	15 (15.2)	22 (15.2)

[a] More than 99 APP with LAI are described on admission, and more than 145 at discharge, as some patients were on more than one LAI. [b]Withdrawn from the Belgian market in October 2018.
LAI ; Long-acting injectable

eTable 3. Description of the ten cases of clozapine introduction during the psychiatric hospitalisations

Patients case	Antipsychotics on admission	Antipsychotics at discharge	Clozapine eligibility
1	Olanzapine Amisulpride	Clozapine Paliperidone LAI	Eligible
2	Aripiprazole	Clozapine Aripiprazole	Eligible
3	Risperidone Zuclopenthixol LAI	Clozapine Paliperidone LAI	Eligible
4	Olanzapine Zuclopenthixol	Clozapine	Eligible
5	Aripiprazole Olanzapine Zuclopenthixol Clotiapine Prothipendyl	Clozapine Olanzapine Aripiprazole Clotiapine Prothipendyl	Eligible
6	Olanzapine	Clozapine Zuclopenthixol	Eligible
7	Risperidone Haloperidol Prothipendyl	Clozapine	Eligible
8	Quetiapine Haloperidol	Clozapine	Not eligible - Minimal dosage of previous trials of antipsychotics not reached
9	Paliperidone	Clozapine Olanzapine	Insufficient information to assess clozapine eligibility
10	Amisulpride Paliperidone Clotiapine	Clozapine Amisulpride Paliperidone Clotiapine	Insufficient information to assess clozapine eligibility

LAI ; Long-acting injectable

Prescribing and deprescribing trends in schizophrenia: an overview of inpatients in Belgium and in the Canadian province of Québec

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ABSTRACT

Although switching to antipsychotic monotherapy improves patient outcomes in schizophrenia, antipsychotic deprescribing is rarely performed and its use varies between countries, as do psychotropic prescribing patterns. This study aims to determine factors associated with antipsychotic deprescribing at discharge after a psychiatric hospitalisation and to compare psychotropic prescribing patterns between Belgium and Québec, Canada. Data on adult inpatients with schizophrenia were collected retrospectively in seven hospitals. At discharge, the number of antipsychotics had decreased in 22.2% of the 63 Canadian patients and 9.9% of the 516 Belgian patients. A number of factors increased the likelihood of antipsychotic deprescribing: a hospitalisation in the Canadian hospital (aOR=4.13, 95% CI 1.48-11.5), living in a residential facility (aOR=2.51, 95% CI 1.05-4.39), ≥2 previous antipsychotic trials (aOR=15.38, 95% CI 3.62-65.36), having an antipsychotic side effect (aOR=1.86, 95% CI 1.01-3.44), and being in a general hospital (aOR=2.28, 95% CI 1.09-4.75). Patients on a long-acting injectable antipsychotic (aOR=0.51, 95% CI 0.26-0.98), with prior clozapine use (aOR=0.36, 95% CI 0.13-0.95), greater antipsychotic exposure (aOR=0.35, 95% CI 0.2-0.61) and more hypno-sedatives (aOR=0.65, 95% CI 0.43-0.98), were less likely to be deprescribed. Specific deprescribing interventions could target patients who are less likely to be deprescribed.

1. INTRODUCTION AND BACKGROUND

Antipsychotic monotherapy is the only licensed type of drug treatment for schizophrenia in Europe and Canada [1,2]. Antipsychotic polypharmacy (APP), i.e. the simultaneous use of two or more antipsychotics by one patient, is common worldwide for treatment augmentation or to treat comorbid psychiatric conditions (e.g. anxiety, sleep disorders)[3-5]. There is no high-quality evidence to support greater efficacy of APP over antipsychotic monotherapy[6-8]. Patients on APP experience more adverse effects than those on antipsychotic monotherapy, show poorer treatment adherence and potentially have a greater risk of hospital readmission, thereby increasing healthcare costs[9-11]. All schizophrenia prescribing guidelines therefore recommend antipsychotic monotherapy for a first episode, and switching to another monotherapy where there is a lack of efficacy or poor tolerability [12]. In situations of treatment resistance, clozapine is the first choice of treatment because of its superior efficacy [13]. Clozapine augmentation with another antipsychotic should only be considered when symptoms persist after an appropriate trial of clozapine, because there is little evidence to support its use [14]. In many cases, other psychotropic medications are also prescribed to patients with schizophrenia. Off-label use of these medications and potentially inappropriate prescribing are common in this population, and increase the risk of medication-related harms, warranting consideration of deprescribing these potentially deleterious treatments [15-17].

Deprescribing is the process of identifying and discontinuing medications for which existing or potential harms outweigh potential benefits within the context of an individual patient's care goals, functioning, values and preferences[18]. While deprescribing may encompass reducing the dose or completely stopping the medication, antipsychotic deprescribing in schizophrenia refers to reducing the number of antipsychotics. Indeed, an appropriate dose of antipsychotics that ensures the blockade of at least 65-70% of D2 receptors is needed to reduce psychotic symptoms. Dose reduction is therefore not always appropriate, especially during an exacerbation (e.g. during acute psychiatric hospitalisation)[19]. Moreover, the

daily dose of antipsychotic cannot be reduced to below a certain threshold during maintenance without recurrence of symptoms and/or rehospitalisation [20]. However, switching from APP to antipsychotic monotherapy leads to improvement in attention and executive functions, and fewer side effects and has been shown to reduce the risk of relapse, possibly by improving treatment adherence [21-23].

Psychotropic prescribing patterns can differ greatly between countries and are influenced by physician preferences, culture, norms and environment (e.g. health system)[24,25]. In the treatment of schizophrenia, APP rates have been reported to be higher in Europe than in North America [5]. Moreover, Canada has been the leader in deprescribing policies in the last few decades, and Canadian researchers have developed several programmes and algorithms for deprescribing psychotropics[26]. A comparison between Belgian prescribing and deprescribing patterns for psychotropic drugs and those of a Canadian hospital could therefore help to identify key differences. This may inspire future policies to improve the use of psychotropics in schizophrenia. In addition, most prior studies have focused on outpatient prescribing patterns and lacked an overview of the deprescribing that occurs during a psychiatric hospitalisation. Identifying patients who are less likely to be deprescribed naturally (i.e. without a specific intervention) could therefore help to develop targeted hospital-based deprescribing strategies.

This study aims: (1) to determine factors associated with antipsychotic deprescribing after a psychiatric hospitalisation, and (2) to compare psychotropic prescribing patterns on admission and at discharge in several Belgian hospitals and a Canadian hospital.

2. MATERIALS AND METHODS

2.1. Setting and data sources

Retrospective data were collected in 2020-2021 in a tertiary care hospital in Montréal, Québec, Canada, and in six Belgian hospitals [27]. Prescribing patterns were extracted from local prescribing software and other

characteristics (e.g. demographics, comorbidities) from patient medical records. All drugs were encoded according to the Anatomical Therapeutic Chemical (ATC) classification.

2.2. Study population

The data extracted concerned individuals between 18 and 64 years old, discharged from psychiatric units after an acute hospitalisation (i.e. less than one year) between November 2018 and November 2019, with a prescription of at least one antipsychotic on admission and a diagnosis of schizophrenia or schizoaffective disorder (DSM-5 295.xx). In the event of multiple hospitalisations during this period, only the last hospitalisation was analysed.

2.3. Factors potentially associated with antipsychotic deprescribing at hospital discharge

A range of factors, in addition to country, were considered to identify patients with a higher probability of antipsychotic deprescribing. Factors for which data were collected include demographics, disease and hospitalisation characteristics, comorbidities, antipsychotic treatment, and co-treatment. These factors were taken into account as they are associated with the use of APP[27,28], and may therefore increase or reduce the likelihood of deprescribing[29]. The full list of these factors is available in the online Appendix (eTable 1).

Low-dose antipsychotics (i.e. clotiapine ≤40 mg, levomepromazine ≤ 100 mg, prothipendyl ≤80 mg, quetiapine ≤50 mg), trazodone ≤100 mg, benzodiazepine receptor agonists (BZRAs), and sedating antihistamines were considered hypno-sedative drugs when taken at night to induce sleep.

Group homes, nursing homes or supervised residential facilities for individuals with mental disorders were referred to as residential facilities.

2.4. Comparison of antipsychotic and psychotropic prescribing patterns at admission and discharge from psychiatric hospitalisation

2.4.1. Antipsychotics

The prevalence of APP was compared between the two countries, both on admission and at discharge from hospital. Low-dose antipsychotics are frequently used for indications other than psychosis, particularly for the management of insomnia. While the combination of an antipsychotic for psychosis with a low-dose sedating one for sleep disorders is technically APP, clinicians do not always consider it as real APP. Thus, the prevalence of patients based on an alternative definition of antipsychotic polypharmacy, excluding patients on this combination, was also examined. Types of antipsychotics and routes of administration were compared. Antipsychotic exposure was expressed using the ratio of the prescribed daily dose (PDD) to the defined daily dose (DDD) of the World Health Organisation. The PDD/DDD ratio was calculated using the sum of the PDD/DDD ratio of each prescribed antipsychotic in case of APP.

2.4.2. Clozapine

Clozapine prescribing patterns on admission and at discharge were also compared. Patients were considered eligible for clozapine if they had an insufficient response to at least two separate trials of an antipsychotic at a minimal dose of 400 mg of chlorpromazine equivalence, for at least six weeks[13]. The prevalence and evolution of clozapine antipsychotic polypharmacy was compared, and is defined as the combination of clozapine with at least one other antipsychotic.

2.4.3. Other psychotropics

The prevalence of antidepressants, mood stabilizers, BZRAs, trazodone or sedating antihistamines and anticholinergics was compared on admission and at discharge. Anticholinergics refer to drugs indicated for the treatment of

extrapyramidal symptoms which are available in either Belgium or Canada (i.e. procyclidine, trihexyphenidyl, biperiden, benztropine).

2.5. Statistical analysis

Quantitative variables between Belgium and Canada were compared with t-tests or Mann-Whitney tests, depending on their distribution. Fisher tests were used to evaluate the difference in categorical variables between Belgium and Canada. Changes in the prevalence of drug prescriptions between admission and discharge were examined with McNemar tests. A multivariable logistic regression was used to identify factors associated with antipsychotic deprescribing after psychiatric hospitalisation, with multiple imputation for missing data. A backward stepwise elimination based on the Akaike information criterion was used to select the final model, in which p-values <0.05 were considered significant. The statistical analyses were performed using R software version 4.0.3.

2.6. Ethics

The study protocol was approved by the central ethics committee of UCLouvain (Belgium), as well as by the ethics committees of each hospital involved (No. 2019/27NOV/530).

3. RESULTS

3.1. Characteristics of the Belgian and Canadian populations

The characteristics of the Canadian (N=63) and Belgian (N=516) populations were very similar, with a mean age of 40 (SD=12), the majority of the patients living in the community (79.4% and 70.4% respectively, p=0.339) and a median length of hospitalisation of 28 (IRQ 15.5-55.5) and 27 (IQR 13-52) days, respectively (p=0.427). However, 81% of the Canadian patients were admitted involuntarily, compared with 20.2% of the Belgian patients (p<0.001). Conversely, 42.3% of the Belgian patients had a legal guardian while 7.9% of the Canadian had one (p<0.001) (Table 1).

Table 1. Characteristics of included patients with schizophrenia or schizoaffective disorder hospitalised in the Belgian and Canadian hospitals

Characteristics	Canadian patients (N=63)† N, (%)	Belgian patients (N=516)† n, (%)	p-value
Sociodemographic characteristics			
Male	39 (61.9)	286 (55.4)	0.349
Female	24 (38.1)	230 (44.6)	
Age (y), mean (SD)	40 (12)	40 (12)	/
Single	39 (61.9)	420 (81.4)	0.269
Living situation			0.339
Residential facility	8 (12.7)	105 (20.3)	
Homeless	5 (7.9)	48 (9.3)	
Living alone or with relatives	50 (79.4)	363 (70.4)	
Legal guardian	5 (7.9)	217 (42.3)	**<0.001**
Unemployed	55 (87.3)	489 (94.8)	0.051
Medical characteristics			
Tobacco smoking	30 (47.6)	348 (67.6)	**0.009**
Alcohol use disorder	20 (31.8)	118 (22.9)	0.12
Substance use disorder	26 (41.3)	183 (35.6)	0.406
History of violent or aggressive behaviour	24 (38.1)	224 (43.6)	0.422
Intellectual disability	2 (3.2)	49 (9.5)	0.103
Prior suicide attempt	14 (22.2)	135 (26.6)	0.869
Illness duration (y), median (IQR)	9 (4-17)	12 (6-20)	0.085
Age of onset (y), median (IQR)	27 (21-32)	24 (19-30)	**0.017**
Hospitalisation characteristics			
Involuntary admission	51 (81)	104 (20.2)	**<0.001**
Length of hospital stay (d), median (IQR)	28 (15.5-55.5)	27 (13-52)	0.427
Antipsychotic adverse effect(s)	21 (33.3)	238 (46.2)	0.06
Primary diagnosis			**0.003**
Schizophrenia	37 (58.7)	398 (77.1)	
Schizoaffective disorder	26 (41.3)	118 (22.9)	

†Data were extracted from one hospital in Montréal, Canada and from 6 Belgian hospitals.

3.2. Factors associated with antipsychotic deprescribing at hospital discharge

Between hospital admission and discharge, 22.2% of the Canadian and 9.9% of the Belgian patients had antipsychotic deprescribing; i.e., a reduction in the number of antipsychotics. In addition, being hospitalised in the Canadian hospital significantly increased the likelihood of antipsychotic deprescribing (adjusted odds ratio (aOR)=4.13, 95% CI 1.48-11.5).

Living in a residential facility (aOR=2.51, 95% CI 1.05-4.39), two or more previous antipsychotic trials (aOR=15.38, 95% CI 3.62-65.36), having an antipsychotic side effect during the hospital stay (aOR=1.86, 95% CI 1.01-3.44), and being hospitalised in a general hospital (aOR=2.28, 95% CI 1.09-4.75) also significantly raised the probability of antipsychotic deprescribing at hospital discharge.

Conversely, patients on a long-acting injectable (LAI) antipsychotic (aOR=0.51, 95% CI 0.26-0.98), with prior clozapine use (aOR=0.36, 95% CI 0.13-0.95), a higher antipsychotic exposure (aOR=0.35, 95% CI 0.2-0.61), and a higher number of hypno-sedative drugs at discharge (aOR=0.65, 95% CI 0.43-0.98) were less likely to be deprescribed (Figure 1).

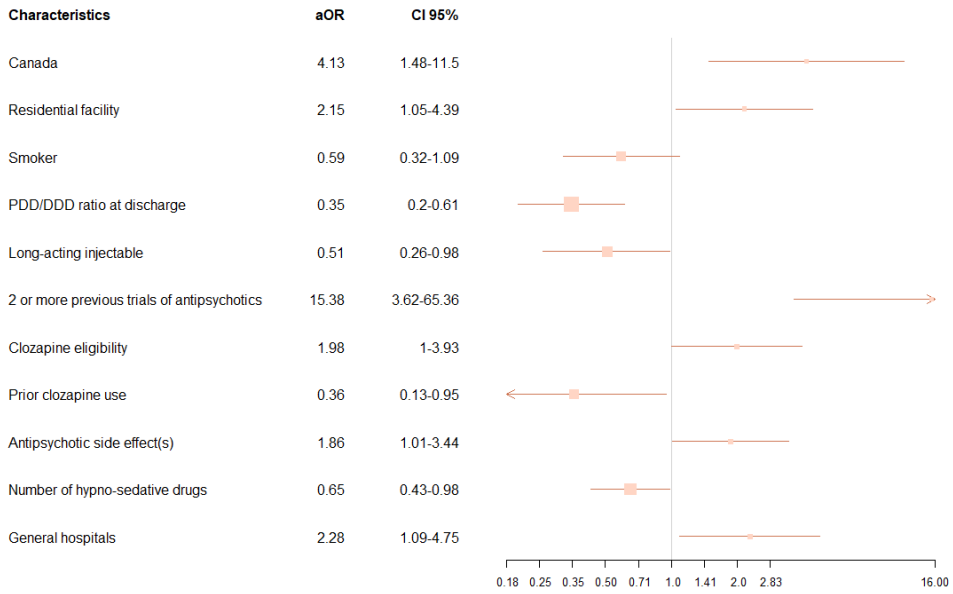

Figure 1. Factors associated with antipsychotic deprescribing at discharge from psychiatric hospitalisations in the multivariable model. aOR, adjusted odds ratio; PDD/DDD, Prescribed Daily Dose on Defined Daily Dose.

3.3. Comparison of psychotropic prescribing patterns

3.3.1. Antipsychotic prescribing patterns

The prevalence of APP was similar in Belgium and Canada on hospital admission (47.9% and 49.2%, respectively, p=0.894)(Table 2). However, 32.3% of the 31 Canadian patients admitted on APP were switched to monotherapy during their stay, while this occurred in only 13.4% of the 247 Belgian patients admitted on APP (p=0.02). The proportion of patients admitted on monotherapy and discharged on APP was not statistically different between hospitals of the two countries (34.2% in Belgium vs. 28.1% in Canada, p=0.9).

The types of antipsychotics used were comparable on admission, but significantly more patients were discharged on a combination of a first-generation antipsychotic with a second-generation antipsychotic in the Belgian hospitals (62.3% of the patients on APP) compared with the Canadian one (30% of the patients on APP) ($p<0.001$) (Table 2).

In addition, more Canadian patients were discharged on an LAI antipsychotic. The majority of those discharged on APP from the Canadian hospital had a combination of an LAI with an oral antipsychotic (86.7%), whereas this type of combination was only prescribed to 46.2% of the Belgian patients discharged on APP ($p<0.001$) (Table 2).

A similar proportion of patients were being treated with clozapine on hospital admission in both populations (11.1% in Canada vs. 9.3% in Belgium, $p=0.648$). Although a comparable proportion of patients were eligible to clozapine in the two countries (39.7% in Canada vs. 28.2% in Belgium, $p=0.775$), significantly more patients had clozapine introduced in Canada (14.3%) than in Belgium (1.9%) ($p<0.001$). This leads to significantly more patients being discharged with clozapine in Canada (23.8%) than in Belgium (11%) ($p=0.007$). In addition, a large majority of patients discharged on clozapine received it in combination with another antipsychotic (80% in Canada vs 75.4% in Belgium ($p=0.011$). Significantly more patients received clozapine in combination with an LAI in Canada than in Belgium (60% vs 36.8% of all patients on clozapine antipsychotic polypharmacy respectively) ($p=0.003$). In both countries, paliperidone was the antipsychotic most frequently combined with clozapine.

Table 2. Antipsychotic prescribing patterns in Belgium and Canada, before and after psychiatric hospitalisations

	Admission			Discharge		
	Canada (N=63)	Belgium (N=516)	p-value	Canada (N=63)	Belgium (N=516)[1]	p-value
APP	31 (49.2%)	247 (47.9%)	0.894	30 (47.6%)	305 (59.1%)	0.081
PDD/DDD	1.7 (IQR 1-2.6)	1.5 (IQR 1-2.3)	0.653	1.8 (IQR 1.1-2.4)	1.8 (IQR 1.1-2.5)	0.662
APP alternative definition	30 (47.6%)	183 (35.5%)	0.072	29 (46%)	227 (44%)	0.789
Number of antipsychotics per patient			0.861			0.062
2 antipsychotics	23 (36.5%)	182 (35.3%)		23 (36.5%)	216 (41.9%)	
3 antipsychotics	7 (11.1%)	57 (11%)		7 (11.1%)	76 (14.7%)	
4 antipsychotics	1 (1.6%)	7 (1.4%)		0	11 (2.1%)	
5 antipsychotics	0	1 (0.2%)		0	2 (0.4%)	
Type of antipsychotics			0.322			**0.002**
Only FGA	7 (11.1%)	41 (7.9%)		8 (12.7%)	45 (8.7%)	
Only SGA	43 (68.3%)	326 (63.2%)		46 (73%)	280 (54.4%)	
FGA+SGA	13 (20.6%)	149 (28.9%)		9 (14.3%)	190 (36.9%)	
At least one FGA	20 (31.7%)	190 (36.8%)	0.489	17 (27%)	235 (45.6%)	**0.005**
At least one SGA	56 (88.9%)	475 (92%)	0.342	55 (87.3%)	470 (91.3%)	0.351
Route of administration			**<0.001**			**<0.001**
Only LAI	18 (28.6%)	98 (19%)		22 (34.9%)	87 (16.9%)	
Only per os	20 (31.7%)	319 (61.8%)		14 (22.2%)	281 (54.6%)	
Per os + LAI	25 (39.7%)	99 (19.2%)		27 (42.9%)	147 (28.5%)	
At least one LAI	43 (68.3%)	197 (38.3%)	**<0.001**	49 (77.8%)	234 (45.4%)	**<0.001**
At least one per os	45 (71.5%)	418 (81%)	0.094	41 (65.1%)	428 (83.1%)	**0.002**

[1]515 patients for type and route of antipsychotics at discharge in the Belgian cohort as one patient discharged without any antipsychotic.

Fisher test for dichotomic variables and Chi² test for categorial variables with more than 2 categories. Mann-Whitney for quantitative with a non-normal distribution, t-test for quantitative with a normal distribution.

Abbreviations: APP, Antipsychotic polypharmacy; PDD, Prescribed daily dose; DDD, Defined daily dose; FGA, First generation antipsychotic; SGA, Second generation antipsychotics, LAI, Long-acting injectable antipsychotics

3.3.2. Other psychotropic and anticholinergic prescribing patterns

Examining the prescriptions of hypno-sedative drugs on admission reveals that 22.1% of the Belgian patients and 1.6% of the Canadian patients had a low-dose antipsychotic for sleep disorders ($p<0.001$), 12.8% and 3.2%, respectively, had trazodone or a sedating antihistamine ($p=0.022$), and 45.5% and 22.2%, respectively, had a BZRA ($p<0.001$). This trend persisted at discharge (Table 2). Furthermore, in Belgium, the prevalence of patients on low-dose antipsychotics used for sleep disorders (22.1% vs. 29.3%, $p<0.001$), on BZRAs (45.5% vs. 54.3%, $p<0.001$) and on mood stabilisers (16.9% vs. 19.6%, $p=0.008$) increased significantly from admission to discharge. No significant change in the prevalence of psychotropic medications was observed after hospitalisation in Canada (Figure 2).

Finally, significantly more Canadian (22.2%) than Belgian patients (9.3%) had an anticholinergic on admission ($p=0.004$), but the prevalence of anticholinergics at discharge decreased significantly in Canada (9.5%) ($p=0.027$) while it increased slightly in Belgium (11.6%) ($p=0.025$), reversing the trend (Figure 2).

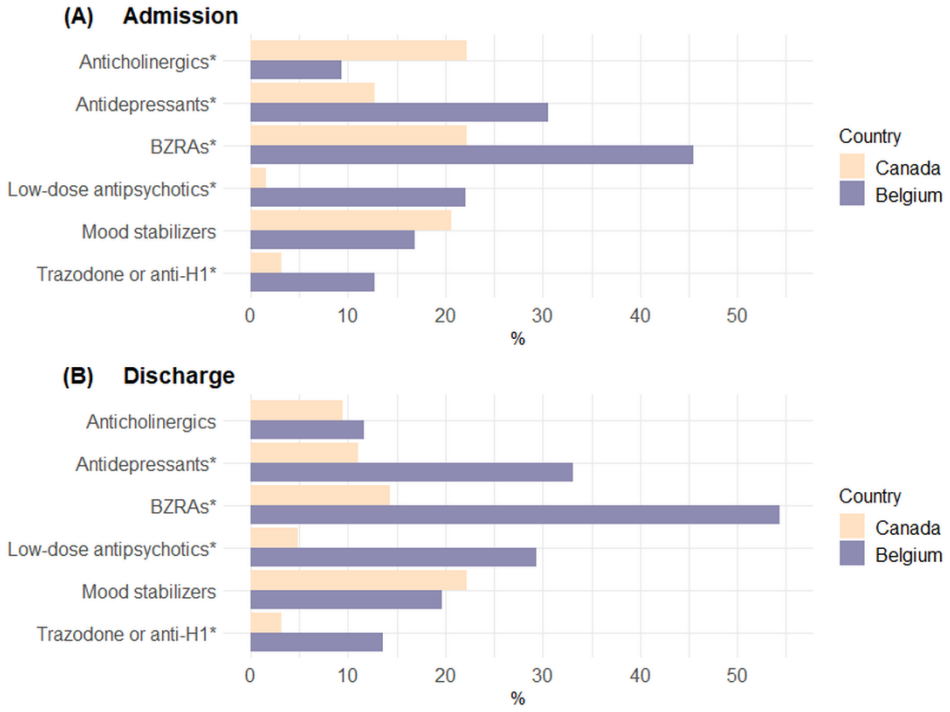

Figure 2. A. Psychotropic prescribing patterns in schizophrenia on admission of psychiatric hospitalisations in Belgium (N=516) and Canada (N=63).

B. Psychotropic prescribing patterns in schizophrenia at discharge from psychiatric hospitalisations in Belgium (N=516) and Canada (N=63).

At hospital admission, anticholinergics (p=0.004), antidepressants (p=0.003), benzodiazepines (p<0.001), low-dose antipsychotics for sleep disorders (p<0.001), and low-dose trazodone or sedating antihistamine (p=0.022) were significantly more prescribed in Belgium than in Canada. At discharge, antidepressants (p<0.001), benzodiazepines (p<0.001), low-dose antipsychotics for sleep disorders (p<0.001), and low-dose trazodone or sedating antihistamines (p=0.014) were significantly more prescribed in Belgium than in Canada. BZRAs, Benzodiazepine receptor agonists; anti-H1, Sedating antihistamines. *Statistically significant difference.

4. DISCUSSION

Differences were identified in prescribing and deprescribing patterns in schizophrenia between the Belgian and Quebec sites, although the characteristics of the two populations were very similar.

Despite the fact that rather more patients were admitted involuntarily in the Canadian hospital, which potentially translates more severe symptoms, a hospitalisation in Canada increases the probability of having an antipsychotic deprescribed and significantly more patients had a switch from APP to monotherapy in this hospital. These findings may suggest that the willingness of clinicians to deprescribe would overcome the barrier of symptom severity. Indeed, patients with schizophrenia are often reluctant to take an antipsychotic, especially when they have a negative attitude toward medication[30] or lack insight[31]. Adherence to antipsychotics is challenging in schizophrenia, with up to 50% of schizophrenic patients being non-adherent[32], and is reduced by polypharmacy[14]. However, some clinicians believe that APP can speed up effect, increase adherence or further reduce psychotic symptoms[4,33], making them more reluctant to deprescribe, especially during the acute psychotic state[33]. The barrier to deprescribing thus appears to be more related to psychiatrists than patients, which is different from what is observed for benzodiazepines, where the barriers come from both sides[34]. However, the patient or family barrier to deprescribing cannot be excluded, and as it has never been specifically addressed in schizophrenia, further studies are needed. Nevertheless, this result may help convince clinicians that deprescribing is a possible option, even for the more severely affected patients. In addition, antipsychotic deprescribing was beneficial for patients, as it was correlated with a lower antipsychotic exposure, which reduces the risk of extrapyramidal symptoms[14]. Patients experiencing antipsychotic side effects were also more likely to have an antipsychotic deprescribed, indicating that prescribers have a good understanding of the increased risk of side effects when using APP. As one of the main causes of non-adherence is adverse effects[35], it would be preferable to progressively deprescribe to reach monotherapy with close

monitoring rather than the patient abruptly stopping all medication. Indeed, deprescribing may improve patient adherence to their sole antipsychotic by reducing the side effect burden[14].

In Belgium, more patients were discharged on a first-generation antipsychotic, and the combination of a first-generation and an atypical antipsychotic was also more frequent among patients on APP. Augmentation with a first-generation antipsychotic reverses the benefit of the atypical antipsychotic in terms of motor adverse effects while exposing patients to the metabolic side effects of the second-generation drug. In addition, there are no significant differences in efficacy between these two classes [13,36-39]. The higher level of prescribing of anticholinergics in Belgium than in Canada and the increase in this measure after psychiatric hospitalisations suggests that there are more motor adverse effects in the Belgian population, presumably induced by the higher rate of first-generation prescribing. Besides, more patients were treated with an LAI antipsychotic in the Canadian hospital than in Belgium. LAI antipsychotics reduce the risk of treatment discontinuation, relapse and hospitalisation in comparison with oral antipsychotics [13,40-43], which is crucial in schizophrenia, because the higher the number of relapses, the worse the patient's psychopathological state will be over time [43]. A prescribing algorithm for LAI antipsychotic treatment in psychosis has been developed in Canada, with recommendations to propose it after a first episode, even to supposedly adherent patients[44]. No such algorithm is available in Belgium however, which could explain this difference. Surprisingly, having an LAI antipsychotic was associated with a lower odds of deprescribing, even though that the majority of patients with schizophrenia can be safely switched to monotherapy without symptoms worsening, especially when the combination involves an LAI antipsychotic [45].

Clozapine is under-prescribed in Belgium compared with Canada, despite being the only antipsychotic registered for the treatment of refractory illness[13,14]. Although a similar proportion of patients were eligible for clozapine in the two countries, more than seven times more patients had clozapine introduced during their stay in the Canadian hospital. Blood

monitoring is often put forward as the main barrier to clozapine introduction, due to patients' reluctance to have blood tests. However, it has not restrained prescribing of clozapine in the Canadian site, even though blood monitoring is mandatory for clozapine to be dispensed by a pharmacist in Canada, which is not the case in Belgium. Furthermore, a large majority of patients on clozapine were being treated with a combination of clozapine and another antipsychotic in both countries, even though this is considered the last-option treatment after an insufficient response to clozapine (i.e. ultra-resistance). Few treatment options have high quality supporting evidence for patients who are ultra-resistant and the majority of the clinical guidelines do not support the use of clozapine antipsychotic polypharmacy [12]. In addition, in both countries, the majority of patients for whom clozapine was introduced for the first time were immediately prescribed clozapine antipsychotic polypharmacy without a prior trial of clozapine monotherapy.

Far more patients were treated with hypno-sedative drugs (e.g. BZRAs, low-dose trazodone) in the Belgian sites than in the Canadian hospital, both on admission and at discharge. BZRAs are often prescribed in a context of psychotic agitation or to induce sedation but their use should be temporary [14], especially as BZRAs augmentation in schizophrenia increases the risks of both suicidal and non-suicidal death, emergency visit, and rehospitalisations [46-49]. Moreover, a larger number of low-dose antipsychotics were prescribed in Belgium compared with Canada for treatment of sleep disorders. Off-label use of antipsychotics is increasing worldwide [50,51], even though the efficacy of adding a low-dose antipsychotic to an antipsychotic at a regular dose to improve sleep has never been studied in patients with schizophrenia. This can expose them to potentially serious adverse effects, such as a neuroleptic malignant syndrome [52]. The benefit-risk ratio for their use as hypno-sedatives is thus uncertain and their use is controversial [53,54]. Non-pharmacological approaches should be prioritised over pharmacological treatment in situations of sleep disorders in schizophrenia [55]. Interestingly, patients on a larger number of hypno-sedative drugs were less likely to have an antipsychotic deprescribed. As hypno-sedative drugs are often prescribed in

situations of agitation, aggressiveness and/or anxiety, prescribing of these drugs may indicate a more complicated clinical context. However, although a higher daily dose of antipsychotics may be temporarily necessary during acute psychotic episodes, the options recommended by the current prescribing guidelines are to choose an antipsychotic with sedating properties or to add a short-term benzodiazepine but not to combine different antipsychotics, and this should not prevent antipsychotic deprescribing [14]. Particular attention should be paid to reducing the number of antipsychotics given to these patients.

Overall, Belgian patients are more exposed to non-evidence-based prescribing patterns of psychotropic drugs than patients in the Canadian hospital. Lower adherence to schizophrenia prescribing guidelines increases healthcare costs and reduces quality-adjusted life-years, in addition to exposing patients to greater risks of adverse effects [56]. As both countries have universal health coverage, medication costs are unlikely to play a major role in these differences. A number of hypotheses can be put forward. First, algorithms aimed at deprescribing psychotropics, such as BZRAs or antipsychotics have been advertised in Canada, but not in Belgium [26]. Promotion of these may have increased awareness of the necessity of deprescribing in Canada, and made psychiatrists more cautious about using antipsychotic polypharmacy. In addition, these different patterns may be due to differences in culture and norms between the two countries, with an evidence-based-medicine practice more common in Canada than in Belgium. A last hypothesis is the presence of a clinical pharmacist in the Canadian team, who may have encouraged deprescribing of antipsychotics and prescribing of clozapine, as well as the rational use of hypno-sedative drugs. Indeed, it is proven that psychiatric clinical pharmacists improve quality of care when included in mental health teams [57], and their interventions in psychiatry are associated with cost avoidance, especially regarding the use of antipsychotics [58]. Such services should therefore be encouraged.

The results of this study should be interpreted within their limitations. Explanatory variables were extracted from medical records. Some

information was not always available if not systematically reported, such as adverse effects or the history and number of previous antipsychotic trials. However, certain variables were dichotomised in the analysis to increase accuracy. Furthermore, the data from the Canadian population come from a single hospital in Québec, and generalisability to the whole situation in Canada cannot be assumed. In a previous study in the province of Ontario, Canada, inpatients with psychotic disorders received fewer LAI antipsychotics than in the Québec hospital, and also less APP, but a similar proportion of first-generation antipsychotics[59]. Moreover, in a national Canadian comparison, the proportion of LAI new starts was much higher in Québec than in other Canadian provinces[60]. Thus, since the treatment on admission reflects prescribing patterns in the outpatient setting, and is therefore not hospital-specific, it is more likely to reflect prescribing patterns in Québec more closely than those in other provinces.

5. CONCLUSION

Antipsychotic deprescribing is already performed in identifiable patients, settings or situations. Patients hospitalised in the Canadian hospital were more likely to be deprescribed than those hospitalised in Belgium. Belgian patients were also more exposed to low-value psychotropic prescribing than Canadian patients. Strategies and interventions should be developed and implemented to improve psychotropic prescribing and encourage antipsychotic deprescribing to achieve antipsychotic monotherapy. More complex deprescribing strategies should target patients who are less likely to be deprescribed.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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APPENDIX

eTable 1. List of factors tested for their potential association with antipsychotic deprescribing

Demographics
Country
Age
Sex
Relationship situation: single or in a relationship
Living situation: homeless, alone or with relatives, residential facility
Having a legal guardian/conservatorship
Being unemployed
Comorbidities
Tobacco smoking
Alcohol use disorder
Substance use disorder (except alcohol)
Intellectual disability
Number of comorbidities
Characteristics of disease
Diagnosis: schizophrenia or schizoaffective disorder
Duration of illness
Age of onset of the illness
Prior suicide attempt(s)
2 or more previous admissions in the year prior to the current hospital stay
GAF score on admission
Having a history or current violent or aggressive behaviour
Hospitalisation characteristics
Length of hospital stay
Involuntary admission
Type of hospital: general or psychiatric
Prescriber status: senior or resident
Antipsychotic treatment
Having at least one long-acting injectable antipsychotic
Having at least one first-generation antipsychotic
Antipsychotic exposition (i.e. PDD/DDD ratio)
2 or more previous trials of different antipsychotics
Prior use of clozapine
Clozapine eligibility
Experiencing an antipsychotic side effect
Administration of an “as needed” antipsychotic during the hospital stay
Co-treatment
Antidepressant
Mood stabilizer (i.e. lithium, valproate, lamotrigine)
Benzodiazepine
Trazodone or sedating antihistamine
Number of psychotropics cotreatment
Number of hypno-sedative drugs
Anticholinergic
Anticholinergic administered during the hospital stay
Daily dose of benzodiazepines received during the hospital stay[†]

CHAPTER I

CHAPTER II

Dissemination of evidence-based practices

CHAPTER II

Assessing the professional social capital of psychiatrists: development of the Resource Generator for Psychiatrists (RG-Psy)

Juliette Lagreula, Vincent Lorant, Olivia Dalleur

Submitted

ABSTRACT

Background: In the field of psychiatry, the dissemination of clinical innovations greatly depends on the social capital of clinicians. An instrument specifically aimed at measuring their professional social capital therefore needs to be developed.

Methods: This survey was conducted to develop and validate the Resource Generator for Psychiatrists, an 11-item questionnaire measuring the social capital of psychiatrists. The online questionnaire was administered through a link sent by e-mail to all psychiatrists and residents in psychiatry licensed to work in Belgium, after excluding ineligible psychiatrists. A total of 1618 psychiatrists or residents were reached. An exploratory factor analysis was conducted. Internal consistency was assessed using Pearson's correlation, item-total correlation and Cronbach's alpha. Test-retest reliability was also measured. Multivariable linear regression analysis assessed the association between the total score of the social capital and psychiatrist demographics.

Results : A total of 196 psychiatrists responded to the survey (response rate: 12.1%). The Resource Generator for Psychiatrists showed a normal distribution with a mean of 23.6 (SD=15.5), good test-retest reliability (ICC=0.81) and a good total Cronbach's alpha (0.74). Exploratory factor analysis revealed two main subtypes in psychiatrists' social capital: "Resources for the clinician" and "Resources for the professional", with a Cronbach's alpha of 0.62 and 0.7 respectively. Clinicians attending institutional seminars (β=5.52, SE=2.2, p=.013) and working in multidisciplinary settings, such as hospitals (β=4.75, SE=2.06, p=.023) or a mobile team (β=8.75, SE=3.52, p=.014) were more likely to have higher social capital.

Conclusion : Psychiatrists' access to professional resources can be reliably measured by using an 11-item questionnaire.

1. BACKGROUND

The psychiatric field is characterised by a low rate of adoption of therapeutic innovations[1,2]. Research findings are not easily incorporated into clinical practice[3], and this lack of adoption limits the impact of new findings on patient outcomes[2]. As a result, suboptimal practice may continue[2]. In order to keep abreast of the latest innovations, clinicians often rely on colleagues, and interpersonal relationships therefore greatly influence the dissemination of innovations[2-4]. Moreover, attitude towards an innovation depends on access to information, but also on social influence from colleagues[3]. Indeed, many clinicians cited their colleagues as the most valued source of information, not only to hear about new findings but also to help them interpret complex cases, or obtain advice[4]. Hence, in the field of mental health, the social capital of psychiatrists is a key resource that needs to be monitored.

The two main methods to measure social capital are the "name generator" and the "position generator". The first consists of mapping an ego-centred social network from an individual's response to a question aimed at identifying who they talk to about a specific topic. The network then expands from this ego to a subsequent inventory of social resource based on the inclusion of names. However, it is not clear whether these relationships are a reliable means of identifying access to resources[5]. The second method represents a collection of resources based on position-related dimensions in a hierarchically modelled society (e.g. highest access prestige), but it has the disadvantage of containing little specific information on the diversity of the resources[5]. The Resource Generator (RG), developed by Snijders and Van Der Gaag, combines the positive aspects of a name generator (i.e. details on the accessed resource) and a position generator (i.e. position-related dimension). The RG consists of a fixed list of resources representing a concrete collection of social capital in different life domains[5]. It examines the availability of each resource by measuring the strength of the link through which the resource is accessed. Social capital as measured by the RG therefore captures the support that an individual can access through their relationships[5,6]. The RG

has been presented as producing better measurements of social capital compared to a position generator alone, because it is based on access to resources rather than hypothetical assistance from people one knows.[6] This questionnaire can be administered quickly and is easily interpreted. However, the RG was developed for the general population, and needs to be validated for different populations[7]. Indeed, the list of resources specific to a professional field – and to psychiatry, in particular – may vary from that of the general population, and it is therefore important to adapt the RG to fit this specific profession.

To the best of our knowledge, no instrument has ever been developed to measure the social capital of psychiatrists. For that reason, creating a specific tool is of particular interest, especially as it may be used to measure the influence of psychiatrists' social capital on several outcomes, such as the adoption of a new innovation.

Our objective is to develop and validate the Resource Generator for Psychiatrists (RG-Psy).

2. METHODS

2.1. Item selection and questionnaire development

The development and validation of the final RG-Psy followed multiple steps.

First, items were selected from the original RG as well as from Webber and Huxley's adaptation for the UK (i.e. Resource Generator UK (RG-UK))[7]. The RG-UK was built according to a rigorous methodology, has good consistency and high reliability. Selected items were then adapted by an expert in the sociology of mental health (VL) to be consistent with the psychiatric profession, in collaboration with a psychiatric clinical pharmacist (JL).

The response categories were also developed on the basis of the RG, the RG-UK and the International Social Survey Programme (ISSP) version[6], following the same steps. Each item has a 6-point response scale and is rated from 0 to 6 according to how close the resource was to the respondent. A cumulative scale, or unipolar scale, was used in the RG and therefore retained in the RG-

Psy, as it is the best model for measuring social capital[5]. Answers were coded "0" when the respondent did not need a certain resource or it was not applicable to their situation, while answering the socially closest resource was coded "6".

Second, the content validity of the draft version was assessed by conducting individual cognitive interviews with an expert panel of six clinicians (e.g. psychiatrists, clinical pharmacists). Cognitive methods aim to determine the process used by respondents to complete the survey[8,9]. The think-aloud strategy is one of the cognitive interview techniques, and was chosen for the development of this questionnaire as it works better for self-administered questionnaires[8]. In this strategy, respondents are asked to think aloud while answering the questions, in order to identify the path leading to their response and to understand the reasons for any misunderstanding and how the question was misunderstood.

2.2. Variables potentially associated with the RG-Psy score

In addition to the RG-Psy, further data were collected, including age, gender, primary spoken language (i.e. Dutch or French), region of practice, practice setting (e.g. hospitals), number of years of practice and status (i.e. psychiatrist or resident in psychiatry).

2.3. Study population

All adult psychiatrists and residents in psychiatry currently working in Belgium were eligible. In order to perform a probability sampling, the federal list of all psychiatrists licensed to work in Belgium was used to identify our target population. In addition, all residents in adult psychiatry were identified by contacting the head of the department of psychiatry in each Belgian medical school. E-mail addresses were obtained through hospital websites or phone calls for psychiatrists working in other settings (e.g. outpatient care).

2.4. Data collection

Our Belgian cross-sectional survey was distributed between April and July 2022 as an online self-administered questionnaire, available in French and

Dutch. A link to the survey was sent by e-mail with personalised invitations. Psychiatry residents were contacted through their supervisors, who forwarded the invitation with a link to the survey. A maximum of three reminders were sent every 7 to 10 days to clinicians who did not complete or open the questionnaire. Data were extracted one month after the last reminder was sent.

2.5. Evaluation of psychometric characteristics

An exploratory factor analysis (EFA) was conducted to assess the structure validity of the scale. EFA aims to identify the underlying dimensions of a domain[10] in order to determine the latent structure of the scale[11]. When different theoretical constructs are identified[10], this indicates the scale is better summarised using subscales[12]. EFA was used instead of confirmatory factor analysis as there was no clear hypothesis regarding the structure of the factors[10,12].

In order to check the appropriateness of carrying out an EFA, the adequacy of the data must be verified. A Kaiser-Meyer-Olkin (KMO) test was used, where a KMO ≥ 0.6 indicates sampling adequacy[13]. Bartlett's test of sphericity was also performed to reject the hypothesis of independence between variables. Finally, inspection of the correlation matrices was undertaken[13].

EFA with maximum likelihood for factor extraction was used, because it is the most appropriate method when the data are relatively normally distributed[11]. The number of factors to be retained was determined using the scree test, which involves examining the graph of eigenvalues of unrotated factors (i.e. the scree plot) and identifying the point where the slope breaks. The number of points above the break determine the number of factors to be retained[10,11,14]. Promax rotation (i.e. oblique method) was used because items were correlated[10,14]. After rotation, items loading ≥0.3 for one factor were kept and grouped with the corresponding factor. Cross-loadings were assessed, and defined as an item loading on more than one factor[14].

Internal consistency was then examined using Cronbach's alpha for each subscale and the total scale, and also using item-total correlation (ITC)[15].

Internal consistency refers to "the extent to which items are correlated (homogeneous), thus measuring the same concept"[12]. A Cronbach's alpha between 0.7 and 0.9 indicates reliable internal consistency[12]. ITC calculates the correlation of each item with the mean total score of the scale[15]. Different threshold values for ITC to keep an item in the scale have been described, mainly 0.2 [16,17] and 0.4[15].

Finally, test-retest reliability was verified using the intra-class correlation (ICC), as this is the most appropriate parameter for continuous measurements[12]. A purposive sample of eight respondents were asked to complete the survey twice at one-week intervals. An ICC above 0.7 is considered reliable[12,17].

2.6. Statistical analysis

The sum of all item responses was used to calculate the total RG-Psy score, which was the dependent variable. A multivariable linear regression model was run with stepwise backward elimination based on the Akaike Information Criterion to select the final model, in which p-values <0.05 were considered significant. Factors included in the initial model are detailed in the Resource (eTable 1). Statistical analysis was conducted using R software version 4.0.3. The packages car, rms, psych and dplyr were used.

2.7. Ethics

This study was approved by the ethics committee of Université Catholique de Louvain (No. 2022/08FEV/055).

Participation was voluntary, and each respondent provided informed consent before completing the questionnaire. Responses were anonymous.

3. RESULTS

3.1. Scale adaptation and cognitive pre-testing

The selection and adaptation of items to match the field of psychiatry resulted in an initial list of 14 items. During the cognitive interviews, some items were considered redundant. These situations were mainly due to the

difficulty of adapting some items to a specific profession. For example, “Give you a good reference for a job” and “Help you to find somewhere to live if you had to move house” had been adapted as “Helping you find another job” and “Helping you find another hospital or workplace”, respectively. These two items were considered redundant by the experts and were merged into a single item: “Helping you find another job or workplace”. Other items were considered irrelevant because they always required the same resource due to the institutional organisation. Some misunderstandings were also identified and the items in question were reworded accordingly. This resulted in a 13-item scale that was used for the survey.

3.2. Characteristics of the study population

After excluding ineligible psychiatrists (eFigure 1 in the Supplementary file), a final population of 1618 psychiatrists and residents was contacted. A total of 196 psychiatrists responded to the survey (response rate: 12.1%). Forty-nine questionnaires were excluded due to failure to complete the RG-Psy, resulting in a total of 147 questionnaires being analysed.

To test for possible inclusion bias, characteristics of the 49 clinicians who did not respond to the RG-Psy were compared with those of the respondents. There were no statistically significant differences in demographic characteristics between clinicians who did not respond and those who completed the questionnaire, with the exception of region of practice. However, the primary spoken language of respondents was similarly distributed in both populations, reflecting a comparable representation of the Belgian population (eTable 2 in the Supplementary file).

The majority of respondents were men (59.2%) with an average of 23.6 (SD=15.5) years of practice. They were equally distributed between the two main language communities (i.e. French-speaking: 52.4%, Dutch-speaking: 47.6%). Prescriber characteristics are summarised in Table 1.

Table 1. Characteristics of the respondents

Characteristics	Total (N=147) n, (%)
Age (y), mean (SD)	51 (16)
Gender	
Women	59 (40.1)
Men	87 (59.2)
Other	1 (0.7)
Primary spoken language	
Dutch	70 (47.6)
French	77 (52.4)
Region	
Brussels	38 (25.9)
Flanders	65 (44.2)
Wallonia	44 (29.9)
Work site	
General hospital	38 (25.8)
Psychiatric hospital	69 (46.9)
Primary care mental health service	27 (18.4)
Mobile team	10 (6.8)
Private practice	71 (48.3)
Prison	5 (3.4)
Residential facility	11 (7.5)
Other	25 (17)
Year of practice, mean (SD)	23.6 (15.5)
Medical resident	26 (17.7)

3.3. Psychometric characteristics

The total RG-Psy score showed a normal distribution, with a mean of 32.5 (SD=12). The percentage of each item response can be found in Table 2.

Table 2. Frequency of response to RG-Psy items (N=147)

RG-Psy subscales and total	% Yes (N=147)	If yes, access through					
		A psychiatrist friend	A fellow psychiatrist	A senior psychiatrist, a supervisor	Another psychiatrist that I know	Another colleague (e.g. nurse, psychologist)	A professional association
Resources for the clinician							
1. Advising you about a patient	95	7	44	16	24	3	1
2. Helping you with patient follow-up if you were unable to work for a few weeks	93	2	64	0	16	4	6
3. Helping you to get a patient admitted to an inpatient or residential unit (e.g. psychiatric care home)	87	3	30	5	44	5	0
8. When you are feeling a bit down	78	46	7	4	7	12	0
9. Be there if you just want to talk about your day	73	21	16	1	1	33	1
Resources for the professional							
6. Helping you find another job or another place to work	62	27	0	3	16	7	9
7. Advising you on your career	67	29	1	16	13	5	3
10. To confirm your skills as a psychiatrist	72	11	20	27	7	3	5

11. Have contacts with federal or regional mental health authorities	79	1	8	17	10	10	33
12. Have contacts with the media (newspapers, radio, television)	54	3	7	15	7	3	18
13. Organising a professional/scientific event	80	4	22	14	12	8	20
Removed items							
4.Helping you with a patient's psycho-social orientation	95	1	11	3	7	69	3
5.Helping you with forensics	96	7	16	23	11	18	21

Structure validity

Data from the RG-Psy are appropriate for conducting an EFA, with good sampling adequacy (KMO test:0.77) and a significant Bartlett's test of sphericity ($p<.001$). The sample size is also appropriate for an EFA, as it followed the rules-of-thumb (i.e. 10 subjects per variable when below 200)[10]. The scree plot suggests a two-factor model (i.e. two subscales). After rotation, two items were freestanding (i.e. not loading with a factor) and were thus discarded. The analysis was re-run and confirmed two subscales, which represent "resources for the clinician" and "resources for the professional", respectively. No item loaded below 0.3 with one factor in the final scale (i.e. after exclusion of the two items), and there was no cross-loading (Figure 1). The two subscales were confirmed by examination of Pearson's correlation matrices, ensuring that items in the same subscales were well correlated and thus measured similar theoretical constructs (eTable 3 in the Supplementary file). The removal of the two items was supported by the inter-item total correlation. Indeed, the items "Helping you with a patient's psycho-social orientation" and "Helping you with forensics" have an ITC of 0.27 (i.e. the

lowest ITC of all items) and 0.4, respectively. As the two main thresholds described for ITC are 0.2 and 0.4, this justifies their removal, as their values fall between these two thresholds, in addition to not loading with any factors. Finally, the total Cronbach's alpha, described thereafter, was not significantly modified by the elimination of these items. All other items had a satisfactory item-total correlation with the mean total score and with the mean score of their factor (Table 3).

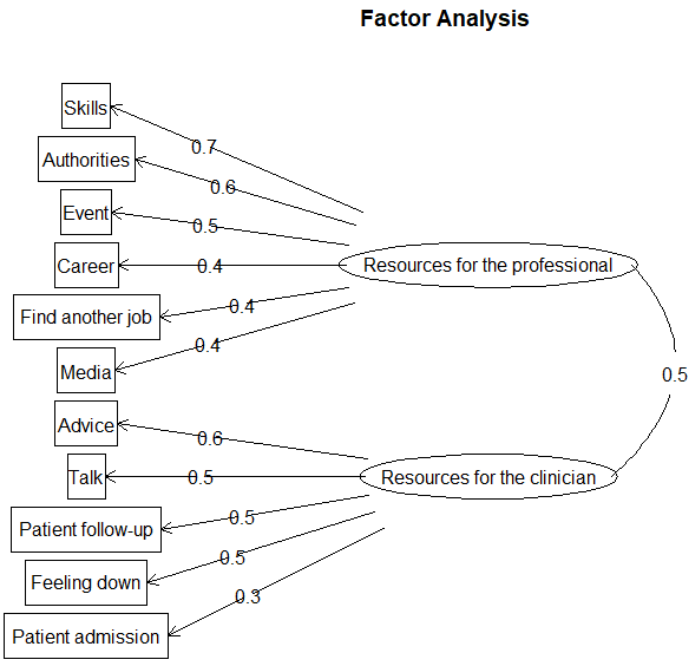

Figure 1. Diagram of the factor analysis of the RG-Psy

Internal consistency

Internal consistency was good for the total scale and for the subscale representing "resources for the professional", with a Cronbach's alpha of 0.74 and 0.7, respectively, and borderline satisfactory for the subscale "resources for the clinician", with a Cronbach's alpha of 0.62 (Table 3).

Test-retest reliability

Finally, the questionnaire showed good test-retest reliability, with an ICC of 0.81.

Table 3. Average score, standard deviation, item-total correlation, and Cronbach's alpha for each item of the final RG-Psy

RG-Psy subscales and total	Mean	SD	Item-total correlation	Item-total correlation with subscale	Cronbach's α
Resources for the clinician					0.62
1. Advising you about a patient	4.0	1.4	0.39	0.52	
2. Helping you with patient follow-up if you were unable to work for a few weeks	4.0	1.7	0.42	0.52	
3. Helping you to get a patient admitted to an inpatient or residential unit (e.g. psychiatric care home)	3.3	1.6	0.33	0.34	
8. When you are feeling a bit down	3.8	2.5	0.53	0.53	
9. Be there if you just want to talk about your day	2.8	2.3	0.49	0.56	
Resources for the professional					0.7
6. Helping you find another job or another place to work	2.5	2.5	0.45	0.46	
7. Advising you on your career	3.0	2.4	0.57	0.55	
10. To confirm your skills as a psychiatrist	3.0	2.2	0.65	0.67	
11. Have contacts with federal or regional mental health authorities	2.0	1.7	0.44	0.53	
12. Have contacts with the media (newspapers, radio, television)	1.6	1.9	0.37	0.41	
13. Organising a professional/scientific event	2.6	2.0	0.41	0.51	
Total					0.74

Abbreviations: SD, Standard Deviation

3.4. Factors associated with the total RG-Psy score

The final multivariable linear regression model revealed that clinicians attending institutional seminars (β=5.52, , Standard Error (SE) =2.2, p=.013) and working in multidisciplinary settings, such as hospitals (β=4.75, SE=2.06, p=.023) or a mobile team (β=8.75, SE=3.52, p=.014), were significantly more likely to have a higher RG-Psy score, translated as greater access to social capital resources. Younger psychiatrists tend to have a lower professional social capital (β=-0.39, SE=0.21, p=.0683) (Table 4).

Table 4. Final multivariable linear regression model of factors associated with the RG-Psy total score

	Coefficient	Standard error	p-value
Age	-0.39	0.21	.068
Years of practice	0.31	0.22	.157
Attendance at institutional seminars	5.52	2.2	**.013**
Attendance at seminars of professional associations	-3.23	1.99	.106
Practice setting			
Hospital	4.75	2.06	**.023**
Mobile team	8.75	3.52	**.014**

p-values<.05, in bold, are considered statistically significant.

4. DISCUSSION

The RG-Psy has been successfully developed and validated, and has good psychometrics characteristics. Although there is some variation in item performance, the good internal consistency suggests that this scale performs well for the target population of psychiatrists.

After careful item selection and adaptation, cognitive pre-testing and exploratory factor analysis, the final scale contains 11 items (final French and Dutch scales shown in eQuestionnaire 1 and eQuestionnaire 2 in the Supplementary file). The EFA revealed two latent dimensions of the RG-Psy. This is different from the original RG and the RG-UK, both of which have four subscales, which seems consistent because both measure access to resources

in the private and professional network, whereas the RG-Psy focuses only on the professional domain.

As a result of the EFA, the item “Helping you with a patient’s psycho-social orientation” was removed, as it did not load with any factors and had the lowest ITC. Access to this resource may be influenced by the availability of institutional solutions, and provides little information on social capital[5]. Indeed, 69% of respondents choose “another colleague (e.g. nurse, psychologist)”, which probably represents a psychologist or social worker. The second discarded item, “Helping you with forensics”, was presumably not very successful, as all response categories were chosen almost equally. Access to this type of expertise (i.e. legal, authorities) was better measured by the item “Have contacts with federal or regional mental health authorities” on the RG-Psy scale (Table 2).

Furthermore, the RG-Psy items display a great diversity in their popularity, i.e. the frequency with which a resource is accessed, demonstrating a reliable scale[5]. Indeed, in a cumulative scale, if only commonly accessed resources are included, meaning that a high percentage give a positive response to the item, minimal levels of trait will be measured, and the scale will be less useful. In the RG-Psy, the least used resource was related to media access, which is similar to the RG, followed by assistance with employment issues (Table 2).

Finally, the multivariable regression model revealed that clinicians working in multidisciplinary settings, such as hospitals or mobile teams, were more likely to have higher social capital. This may mean that clinicians with higher social capital choose these settings, or that these settings increase social integration within the professional network. Young psychiatrists tend to have lower professional social capital, which may be explained by the fact that their social network is still developing. This is the opposite of what was found in the RG-UK, but it seems consistent because in private life, young adults tend to have greater social capital, which is not the same situation as in the professional field.[7]

The strength of the RG-Psy lies in its development and validation according to a rigorous methodology, resulting in a scale with good consistency and reliability. Moreover, the respondents came from all regions of Belgium, were equally divided between the two main Belgian language communities and were well distributed across all workplaces. Finally, our sample size allows sufficient power to calculate parametric properties. However, this scale must be used in the light of certain limitations. First, the rather low response rate of 12.1% could limit generalisability. Physicians are known for not responding well to online questionnaires, generally achieving a lower response rate than other populations[18,19], due to lack of time and survey burden[20]. Moreover, psychiatrists have the lowest response rate of all specialists[20]. In addition, no monetary incentives were used, although they have been shown to increase the response rate of physicians[20,21]. Nevertheless, recent research has established that there is little relationship between a low response rate and biased results, and that a higher response rate does not protect against biased results[22,23]. Indeed, in a previous survey, the exclusion of late and difficult-to-reach respondents did not produce a significant difference in the survey results[23]. It is therefore more appropriate to compare the characteristics of non-respondents with those of respondents. Our analysis indicates that non-respondents do not differ from respondents in their demographics.

5. CONCLUSION

Psychiatrists' access to professional resources can be reliably measured by means of an 11-item questionnaire that can be used to identify how social capital contributes to the dissemination and adoption of best practices in psychiatry.

Ethics approval and consent to participate

This study was approved by the ethics committee of Université Catholique de Louvain (No. 2022/08FEV/055) and performed in accordance with the Belgian privacy legislation of 30 July 2018 and with the European General Data Protection Regulation [GDPR] of 25 May 2018.

Participation was voluntary, and each respondent provided informed consent before answering the questionnaire. Responses were anonymous.

Availability of data and materials

The dataset generated and analysed during the current study are not publicly available due privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JL and VL conceived and designed the study. JL acquired the data and performed the analysis. All authors contributed to the interpretation of the findings. JL wrote the original draft. All authors reviewed, edited, and approved the final content of the manuscript.

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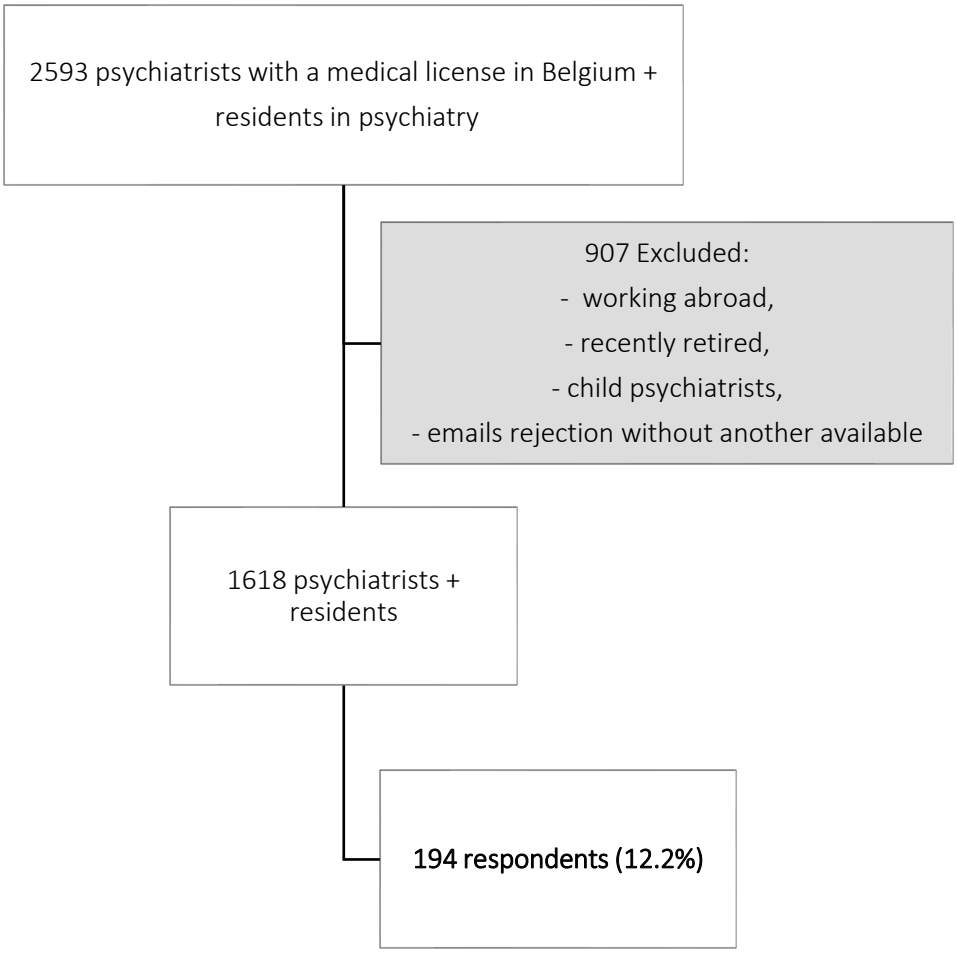
APPENDIX



eFigure 1. Flowchart of survey inclusion and response

eTable 1. Factors included in the multivariable regression model

Gender: women, men, other
Age (years)
Years of practice
Resident in psychiatry
Region of practice: Brussels, Flanders, Wallonia
Attendance at institutional seminars
Attendance at seminars of pharmaceutical industry
Attendance at professional association seminars
Attendance at French/Dutch speaking congresses
Attendance at international English-speaking congresses
Workplace: hospital, mobile team, outpatient care, residential facility

eTable 2. Characteristics of the population of respondents and of non-respondents

Characteristics	Respondents (n=147) n, (%)	Non-respondents (n=49) n, (%)	p-value
Age (y), mean (SD)	51 (16)	48 (18)	0.305
Gender			
Women	59 (40.1)	9 (18.4)	
Men	87 (59.2)	40 (81.6)	0.49
Other	1 (0.7)	0	
User language			
Dutch	70 (47.6)	30 (61.2)	0.137
French	77 (52.4)	19 (38.8)	
Region			
Brussels	38 (25.9)	16 (33.3)	
Flanders	65 (44.2)	28 (58.3)	0.01
Wallonia	44 (29.9)	4 (8.3)	
Workplace			
General hospital	38 (25.8)	10 (20.4)	
Psychiatric hospital	69 (46.9)	27 (55.1)	
Primary care mental health service	27 (18.4)	9 (18.4)	
Mobile team	10 (6.8)	3 (6.1)	0.3
Private practice	71 (48.3)	22 (44.9)	
Prison	5 (3.4)	2 (4)	
Residential facility	11 (7.5)	5 (10.2)	
Other	25 (17)	5 (10.2)	
Years of practice, mean (SD)	23.6 (15.5)	21 (18)	0.332
Medical resident	26 (17.7)	14 (28.6)	0.107
University of graduation			
Universiteit Antwerpen	7 (4.8)	4 (8.3)	
UGent	14 (9.5)	3 (6.2)	
KULeuven	43 (29.3)	21 (43.7)	
UCLouvain	38 (25.9)	8 (16.7)	0.181
ULB	17 (11.6)	1 (2.1)	
ULiege	10 (6.8)	9 (18.8)	
VUB	6 (4.1)	0 (0)	
Other	12 (8.2)	2 (4.2)	

eTable 3. Correlation matrices of the RG-Psy items

RG-Psy subscales and total	Resources for the clinician					Resource for the professional					
	1	2	3	8	9	6	7	10	11	12	13
Resources for the clinician											
1. Advising you about a patient	1										
2. Help you with patient follow-up if you were unable to work for a few weeks	**0.37**	1									
3. Helping you to get a patient admitted to an inpatient or residential unit (e.g. psychiatric care home)	**0.23**	**0.21**	1								
8. When you are feeling a bit down	**0.21**	**0.23**	0.17	1							
9. Be there if you just want to talk about your day	**0.26**	**0.27**	0.14	**0.45**	1						
Resource for the professional											
6. Help you find another job or another place to work	0.06	0.15	**0.21**	**0.22**	0.17	1					
7. Advising you on your career	0.18	0.19	0.17	**0.37**	**0.21**	**0.35**	1				
10. To confirm your skills as a psychiatrist	0.19	**0.23**	0.17	**0.33**	**0.22**	**0.3**	**0.39**	1			
11. Have contacts with federal or regional mental health authorities	0.06	0.13	0.06	0.08	0.18	**0.22**	**0.23**	**0.48**	1		
12. Have contacts with the media (newspapers, radio, television)	0.14	0.12	0.09	0.05	0.17	0.21	0.17	**0.24**	**0.23**	1	
13. Organising a professional/scientific event	0.04	0.02	0.06	0.21	0.13	0.19	**0.33**	**0.33**	**0.25**	**0.3**	1
Total											

Pearson correlation, bold if p-value<0.01

eQuestionnaire 1. Finale French version of the RG-Psy

Les propositions suivantes ont pour but de savoir vers qui vous vous tourneriez pour obtenir de l'aide, si vous en aviez besoin, dans différentes situations. S'il y a plusieurs personnes vers lesquelles vous êtes également susceptibles de vous tourner, choisissez celle qui vous semble la plus proche.

Pour chaque situation, veuillez cocher la case pour indiquer vers qui vous vous tourneriez en premier pour vous aider.

- **Vous conseiller à propos d'un patient**
  a. Un(e) psychiatre ami(e) proche
  b. Un(e) collègue psychiatre sur mon lieu de travail
  c. Un(e) psychiatre sénior, un superviseur
  d. Un(e) confrère/ consœur psychiatre que je connais
  e. Un autre collègue de mon lieu de travail (ex : infirmier, psychologue, secrétaire médicale)
  f. Une association professionnelle
  g. Aucun
  h. Ne sais pas choisir

- **Vous aider dans le suivi des patients si vous étiez en incapacité de travailler pendant quelques semaines**
  a. Un(e) psychiatre ami(e) proche
  b. Un(e) collègue psychiatre sur mon lieu de travail
  c. Un(e) psychiatre sénior, un superviseur
  d. Un(e) confrère/ consœur psychiatre que je connais
  e. Un autre collègue de mon lieu de travail (ex : infirmier, psychologue, secrétaire médicale)
  f. Une association professionnelle
  g. Aucun
  h. Ne sais pas choisir

- **Vous aider à faire admettre un patient dans une unité d'hospitalisation ou résidentielle (ex : maison de soins psychiatriques)**
  a. Un(e) psychiatre ami(e) proche
  b. Un(e) collègue psychiatre sur mon lieu de travail
  c. Un(e) psychiatre sénior, un superviseur
  d. Un(e) confrère/ consœur psychiatre que je connais
  e. Un autre collègue de mon lieu de travail (ex : infirmier, psychologue, secrétaire médicale)
  f. Une association professionnelle
  g. Aucun
  h. Ne sais pas choisir

- **Vous aider à trouver un autre emploi ou un autre lieu de travail**
  a. Un(e) psychiatre ami(e) proche
  b. Un(e) collègue psychiatre sur mon lieu de travail

c. Un(e) psychiatre sénior, un superviseur
d. Un(e) confrère/ consœur psychiatre que je connais
e. Un autre collègue de mon lieu de travail (ex : infirmier, psychologue, secrétaire médicale)
f. Une association professionnelle
g. Aucun
h. Ne sais pas choisir

- **Vous conseiller sur votre carrière**
  a. Un(e) psychiatre ami(e) proche
  b. Un(e) collègue psychiatre sur mon lieu de travail
  c. Un(e) psychiatre sénior, un superviseur
  d. Un(e) confrère/ consœur psychiatre que je connais
  e. Un autre collègue de mon lieu de travail (ex : infirmier, psychologue, secrétaire médicale)
  f. Une association professionnelle
  g. Aucun
  h. Ne sais pas choisir

- **Dans les moments où vous vous sentez un peu abattu**
  a. Un(e) psychiatre ami(e) proche
  b. Un(e) collègue psychiatre sur mon lieu de travail
  c. Un(e) psychiatre sénior, un superviseur
  d. Un(e) confrère/ consœur psychiatre que je connais
  e. Un autre collègue de mon lieu de travail (ex : infirmier, psychologue, secrétaire médicale)
  f. Une association professionnelle
  g. Aucun
  h. Ne sais pas choisir

- **Être là si vous voulez juste parler de votre journée**
  a. Un(e) psychiatre ami(e) proche
  b. Un(e) collègue psychiatre sur mon lieu de travail
  c. Un(e) psychiatre sénior, un superviseur
  d. Un(e) confrère/ consœur psychiatre que je connais
  e. Un autre collègue de mon lieu de travail (ex : infirmier, psychologue, secrétaire médicale)
  f. Une association professionnelle
  g. Aucun
  h. Ne sais pas choisir

- **Vous confirmer dans vos compétences de psychiatre**
  a. Un(e) psychiatre ami(e) proche
  b. Un(e) collègue psychiatre sur mon lieu de travail
  c. Un(e) psychiatre sénior, un superviseur
  d. Un(e) confrère/ consœur psychiatre que je connais
  e. Un autre collègue de mon lieu de travail (ex : infirmier, psychologue, secrétaire médicale)

f. Une association professionnelle
g. Aucun
h. Ne sais pas choisir

- **Avoir un contact avec les autorités fédérales ou régionales de santé mentale**
  a. Un(e) psychiatre ami(e) proche
  b. Un(e) collègue psychiatre sur mon lieu de travail
  c. Un(e) psychiatre sénior, un superviseur
  d. Un(e) confrère/ consœur psychiatre que je connais
  e. Un autre collègue de mon lieu de travail (ex : infirmier, psychologue, secrétaire médicale)
  f. Une association professionnelle
  g. Aucun
  h. Ne sais pas choisir

- **Avoir des contacts avec les médias (journaux, radio, télévision)**
  a. Un(e) psychiatre ami(e) proche
  b. Un(e) collègue psychiatre sur mon lieu de travail
  c. Un(e) psychiatre sénior, un superviseur
  d. Un(e) confrère/ consœur psychiatre que je connais
  e. Un autre collègue de mon lieu de travail (ex : infirmier, psychologue, secrétaire médicale)
  f. Une association professionnelle
  g. Aucun
  h. Ne sais pas choisir

- **Organiser un événement professionnel/scientifique**
  a. Un(e) psychiatre ami(e) proche
  b. Un(e) collègue psychiatre sur mon lieu de travail
  c. Un(e) psychiatre sénior, un superviseur
  d. Un(e) confrère/ consœur psychiatre que je connais
  e. Un autre collègue de mon lieu de travail (ex : infirmier, psychologue, secrétaire médicale)
  f. Une association professionnelle
  g. Aucun
  h. Ne sais pas choisir

eQuestionnaire 2. Finale Dutch version of the RG-Psy

De volgende uitspraken zijn bedoeld om na te gaan tot wie u zich richt als u hulp nodig hebt in verschillende situaties. Als er meerdere mogelijkheden in aanmerking komen, kiest u de meest waarschijnlijke optie.

Vink voor elke situatie aan tot wie u zich als eerste zou richten voor hulp.

- **Voor advies over een patiënt**

a. Een bevriende psychiater
b. Een collega-psychiater op het werk
c. Een senior- of hoger geplaatste psychiater
d. Een collega-psychiater die ik ken
e. Een andere collega op het werk (bv. verpleegkundige, psycholoog, medisch administratief medewerker)
f. Een vakvereniging
g. Geen
h. Ik kan niet kiezen

• **Voor hulp bij de follow-up van patiënten als u enkele weken lang niet kunt werken**

a. Een bevriende psychiater
b. Een collega-psychiater op het werk
c. Een senior- of hoger geplaatste psychiater
d. Een collega-psychiater die ik ken
e. Een andere collega op het werk (bv. verpleegkundige, psycholoog, medisch administratief medewerker)
f. Een vakvereniging
g. Geen
h. Ik kan niet kiezen

• **Voor hulp bij het opnemen van een patiënt in een ziekenhuis of residentiële omgeving (bv. psychiatrisch verzorgingstehuis)**

a. Een bevriende psychiater
b. Een collega-psychiater op het werk
c. Een senior- of hoger geplaatste psychiater
d. Een collega-psychiater die ik ken
e. Een andere collega op het werk (bv. verpleegkundige, psycholoog, medisch administratief medewerker)
f. Een vakvereniging
g. Geen
h. Ik kan niet kiezen

• **Voor hulp bij het vinden van nieuw werk of een andere locatie om aan de slag te gaan**

a. Een bevriende psychiater
b. Een collega-psychiater op het werk
c. Een senior- of hoger geplaatste psychiater
d. Een collega-psychiater die ik ken
e. Een andere collega op het werk (bv. verpleegkundige, psycholoog, medisch administratief medewerker)
f. Een vakvereniging
g. Geen
h. Ik kan niet kiezen

• **Voor loopbaanadvies**

a. Een bevriende psychiater

b. Een collega-psychiater op het werk
c. Een senior- of hoger geplaatste psychiater
d. Een collega-psychiater die ik ken
e. Een andere collega op het werk (bv. verpleegkundige, psycholoog, medisch administratief medewerker)
f. Een vakvereniging
g. Geen
h. Ik kan niet kiezen

- **Voor momenten waarop u zich neerslachtig voelt**
  a. Een bevriende psychiater
  b. Een collega-psychiater op het werk
  c. Een senior- of hoger geplaatste psychiater
  d. Een collega-psychiater die ik ken
  e. Een andere collega op het werk (bv. verpleegkundige, psycholoog, medisch administratief medewerker)
  f. Een vakvereniging
  g. Geen
  h. Ik kan niet kiezen

- **Voor als u gewoon even wilt praten over uw dag**
  a. Een bevriende psychiater
  b. Een collega-psychiater op het werk
  c. Een senior- of hoger geplaatste psychiater
  d. Een collega-psychiater die ik ken
  e. Een andere collega op het werk (bv. verpleegkundige, psycholoog, medisch administratief medewerker)
  f. Een vakvereniging
  g. Geen
  h. Ik kan niet kiezen

- **Om uw competenties als psychiater te bevestigen**
  a. Een bevriende psychiater
  b. Een collega-psychiater op het werk
  c. Een senior- of hoger geplaatste psychiater
  d. Een collega-psychiater die ik ken
  e. Een andere collega op het werk (bv. verpleegkundige, psycholoog, medisch administratief medewerker)
  f. Een vakvereniging
  g. Geen
  h. Ik kan niet kiezen

- **Om contact op te nemen met de federale of gewestelijke instanties inzake geestelijke gezondheidszorg**
  a. Een bevriende psychiater
  b. Een collega-psychiater op het werk
  c. Een senior- of hoger geplaatste psychiater
  d. Een collega-psychiater die ik ken

e. Een andere collega op het werk (bv. verpleegkundige, psycholoog, medisch administratief medewerker)
f. Een vakvereniging
g. Geen
h. Ik kan niet kiezen

- **Om contact op te nemen met de media (kranten, radio, televisie)**
  a. Een bevriende psychiater
  b. Een collega-psychiater op het werk
  c. Een senior- of hoger geplaatste psychiater
  d. Een collega-psychiater die ik ken
  e. Een andere collega op het werk (bv. verpleegkundige, psycholoog, medisch administratief medewerker)
  f. Een vakvereniging
  g. Geen
  h. Ik kan niet kiezen

- **Om een professioneel/wetenschappelijk evenement te organiseren**
  a. Een bevriende psychiater
  b. Een collega-psychiater op het werk
  c. Een senior- of hoger geplaatste psychiater
  d. Een collega-psychiater die ik ken
  e. Een andere collega op het werk (bv. verpleegkundige, psycholoog, medisch administratief medewerker)
  f. Een vakvereniging
  g. Geen
  h. Ik kan niet kiezen

Influence of social capital and general EBM-orientation on psychiatrists' attitude toward antipsychotic polypharmacy in schizophrenia

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In preparation

ABSTRACT

Introduction: Up to half of patients with schizophrenia are treated with antipsychotic polypharmacy despite showing no superiority of efficacy over monotherapy. The aim of this study is to detect factors (i.e. social capital, general EBM-orientation, demographics) associated with a more EBM attitude toward the use of antipsychotic polypharmacy in schizophrenia.

Methods: First, the Knowledge and Attitude scale toward Antipsychotic Polypharmacy in Schizophrenia (KAAPS) was developed in several steps and pre-tested. The questionnaire also contains a measure of professional social capital (Resource Generator for Psychiatrists), a scale of intrinsic EBM-orientation (Evidence-Based Practice Attitude Scale (EBPAS), Aaron et al. 2004) and demographics. The web survey was distributed via a link sent by email to the 1618 eligible psychiatrists and residents in psychiatry of Belgium. Psychometric characteristics of the KAAPS were measured to ensure validity. Factors potentially associated with the KAAPS score were tested.

Results: A total of 196 psychiatrists responded to the survey (response rate: 12.1%). The KAAPS scale shows good psychometric characteristics. The mean KAAPS score, ranked from 0 to 102, was 55.8 (SD=13.7) indicating a tendency toward a more evidence-based knowledge and attitude across respondents. Psychiatrists with higher professional social capital (β= -0.254, SE=0.095, p<0.01), working in a non-multidisciplinary setting (i.e. private practice, primary mental health services, prison) (β=-9.144, SE=2.395, p<0.001), belonging to the Dutch-speaking community (β=-5.133,, SE=2.418, p=0.036) and prescribing a higher percentage of APP (β=-0.194, SE=0.036, p<0.001) were significantly less likely to adopt an evidence-based attitude toward APP. On the other hand, practising cognitive behavioural therapy (β=6.366, p<0.01) increased the KAAPS scores, while intrinsic EBM orientation was not significantly associated (β=0.231, p=0.083).

Conclusion: Social capital influences attitude toward the use of antipsychotic polypharmacy in schizophrenia. Implementation strategies using the social capital of clinicians should be considered to reduce the use of APP in schizophrenia.

CHAPTER II

1. INTRODUCTION

Up to half of patients with schizophrenia are treated with antipsychotic polypharmacy (APP), i.e. two or more antipsychotics[1,2], despite not showing superiority of efficacy over monotherapy[3,4]. APP induces more side effects, reduces treatment-adherence and some combinations even lead to a higher risk of rehospitalisation, which increases health care costs, making its widespread use problematic[5-8]. Clinical prescribing guidelines for schizophrenia, based on these evidences, recommend the sole use of antipsychotic monotherapy in the treatment of schizophrenia[9,10]. A variety of reasons can explain the recourse to APP, including an attempt to further reduce symptoms or to treat a comorbid condition[11,12].

Clinical practice should be based on the best available evidence applied to the individuality of each patient. However, research findings are not always translated into practice, and many treatments used in clinical routine are not supported by strong evidence of efficacy or effectiveness[13]. The increasing amount of medical literature, combined with the limited time available to clinicians makes it difficult to keep up to date. Thus, clinicians often rely on discussion with colleagues to stay aware of the latest innovations or to help them interpreting new evidence[14], especially when scientific findings are complex or controversial[15]. In addition, the psychiatric field has benefitted from high quality evidence later than other field such as oncology, which may have delayed the propensity to adopt innovations such as a new guideline or a new drug[15].

Social influence can modify attitude and prescribing behaviour, and depends on the social capital of each clinician[16]. Indeed, the influence of colleagues has been recognised by psychiatrists themselves as a factor impacting their decision to prescribe APP[17]. Two main theories have emerged to explain how the clinician network exerts this influence. The first, supported by Coleman et al[18], suggests that the more socially connected the clinician (i.e. the wider their network), the more likely they are to adopt the innovation. However, the second theory, known as the theory of structural holes, suggests that the

structure of the network is more important than its size, and that the denser the network, the less new information can penetrate it[16]. This may be because cohesive groups are effective at exerting normative pressure to conform, and new information from outside the network must first penetrate it. This theory would mean that clinicians who have more contacts outside the network will be more likely to come in contact with innovations and adopting them, while those who are the most socially integrated into the network will be less likely to adopt innovations[16]. Nevertheless, given the influence of social capital on clinical practice, it is important to measure its impact on the attitude toward antipsychotic polypharmacy.

Besides, another important factor to consider is the individual difference of clinicians, especially their intrinsic orientation toward evidence-based medicine (EBM)[13].

To the best of our knowledge, no previous studies have focused on these dimensions to understand factors associated with psychiatrists' attitude toward prescribing behaviour, such as antipsychotic polypharmacy. The study of these factors is an important matter considering the high rate of APP prescribing worldwide, and the high prevalence in Belgium[19] provides an opportunity to study this issue.

Our study aims at : 1) Identifying psychiatrists' attitude toward the use of antipsychotic polypharmacy in the treatment of schizophrenia, 2) Detecting factors (e.g. social capital, demographics, intrinsic orientation toward EBM) associated with a more evidence-based attitude toward APP.

2. METHODS

2.1 Development of the Knowledge and Attitude scale toward Antipsychotic Polypharmacy in Schizophrenia (KAAPS)

The KAAPS scale was developed in several steps. First, the most frequent justifications for APP were identified in the literature [11,12,20-23]. We choose to focus on APP not involving clozapine, as recent data suggest that clozapine augmentation with aripiprazole may reduce psychiatric re-hospitalisations[3].

Clozapine, unlike other antipsychotics, is efficient by blocking less than the normally required 60% of D2 receptors[24,25] and also regulates the glutamatergic transmission[26]. Clozapine is reserved for the treatment of refractory illness and clozapine augmentation can only be used in situation of ultra-resistance (i.e. resistance to clozapine)[9,10]. Because of these different modes of action and indications, we chose to study the most common use of APP, i.e. two or more non-clozapine antipsychotics.

The robustness of evidence for each justification for APP was assessed using clinical guidelines or high-quality meta-analysis, where appropriate. An initial list of 16 items was elaborated. A cognitive testing with a panel of six experts (i.e. psychiatrists and clinical pharmacists) was performed to identify misunderstandings and significant problems, ensuring content validity[27]. Some items were modified accordingly, and one item was added, resulting in a 17-item scale. In the final KAAPS, each response was rated on a 7-point bipolar Likert scale (0= Don't know, 1 = totally agree, 2 = agree, 3 = rather agree, 4 = rather disagree, 5= disagree and 6 = strongly disagree). The total KAAPS score was calculated as the sum of each item, with reverse coding where appropriate. Indeed, some items were reversed to avoid the "yea saying"; i.e. the tendency to agree more than disagree[28].

The psychometric properties of the scale were assessed and tests performed are described on 2.5. Statistical analysis. The score ranges from 0 to 102, with the highest score indicating the most evidence-based attitude toward APP.

2.2 Factors potentially associated with the KAAPS score

The Resource Generator for Psychiatrists (RG-Psy) has been used to measure the social capital of psychiatrists, and its potential association with the KAAPS score; i.e. psychiatrists' attitude toward antipsychotic polypharmacy in schizophrenia (Lagreula et al. Submitted). The RG-Psy consists of a fixed list of resources representing a concrete collection of social capital in the professional field of psychiatry. It measures the strength of the link through which different resources are accessed for several purposes in the

professional practice of psychiatry. Development and validation of this scale has been described previously (Lagreula et al. Submitted).

The Evidence-Based Practice Attitude Scale (EBPAS) aims at measuring the four dimensions explaining attitude toward evidence-based medicine (EBM) in general among mental health providers[13]. These four dimensions cover the appeal of innovations, i.e, influence of attractiveness by the way the information is given, the requirement by authorities or supervisors and response of the clinician to these requirements, openness in general and divergence[13]. Divergence appears when the difference between the current practice and the new one is perceived as coming from another culture (e.g. the culture of research) [13]. Indeed, innovations can less likely spread when it has to cross different organisations or professional boundaries, such as recommendations coming from researchers to more practicing clinicians that can hamper their diffusion depending on the personality of each clinician[29]. The EBPAS was another factor tested for its potential association with the KAAPS total score.

Finally, demographic data and individual factors were also collected to take into account their potential co-influence on the KAAPS score, and include age, gender, primary spoken language (i.e. Dutch or French), type of psychotherapy the most often used, practice setting, years of practice (eTable 1 in Supplementary materials).

2.3. Study population and data collection

Psychiatrists and residents in psychiatry working in Belgium were eligible for the survey. The public list of the Belgian federal agency for health, food chain safety and environment recording all psychiatrists licensed to work in Belgium was used to identify our population of interest. Residents in psychiatry were contacted through the head of the department of psychiatry of each Belgian medical school.

This cross-sectional survey was distributed between April and July 2022 as an online-self completion questionnaire, available in French and Dutch and accessible through a link sent by email.

2.5. Statistical analysis

The structure validity of the KAAPS scale was assessed by conducting an exploratory factor analysis (EFA), which aims to determine the theorical construct of the scale, i.e. the presence of subscales[30,31]. A Kaiser-Meyer-Olkin (KMO) test and a Barlett's test of sphericity were performed to confirm the appropriateness of conducting an EFA, where a KMO ≥ 0.6 indicates sampling adequacy and a p-value < 0.5 in the Barlett's test rejects the hypothesis of independence between variables[32]. EFA with a maximum likelihood for factor extraction was used as data are normally distributed[31] and a scree test was executed to determine the number of factors to retain[30,31,33]. Promax rotation was employed as the different dimensions of EBM were expected to be correlated, and items loading ≥0.3 after rotation for one factor were grouped with the corresponding factor[30,33]. Internal consistency was tested with Cronbach's alpha for each subscale and for the total KAAPS scale, as well as with item-total correlation (ITC)[28]. Cronbach's alpha between 0.7 and 0.9 indicate reliable consistency, and items with an ITC beyond 0.4 were kept [28,34]. Test-retest reliability was also ensured with a purposing sample of 8 respondents who complete the survey twice at one-week intervals, enabling the calculation of an intra-class correlation (ICC) where an ICC > 0.7 is considered reliable[34].

The sum of each item response of the KAAPS scale was the dependant variable. Items were rated so that the higher the score, the more evidence-based the attitude. A multivariable linear regression model was performed with stepwise backward elimination based on the Akaike Information Criterion to select the final model, in which p-values <0.05 were considered significant. Casewise deletion was performed for missing values as accounting for a low percentage of the total data, therefore not requiring imputation, and because imputation lowered the fit of the model. Statistical analysis was performed using R software version 4.0.3.

2.6 Ethics

This study was approved by the ethics committee of UCLouvain (No. 2022/08FEV/055). Participation was voluntary, and each respondent provided informed consent before answering the questionnaire. Responses were anonymous.

3. RESULTS

3.1 Characteristics of the study population

After excluding ineligible psychiatrists (eFigure 1 in the Supplement), a final population of 1618 psychiatrists and residents was contacted. A total of 196 psychiatrists responded to the survey (response rate: 12.1%), but 44 questionnaires were excluded due to markedly incomplete data (i.e. only demographic data available), resulting in the analysis of 152 questionnaires.

Respondents were predominantly men (59.2%, n=90), evenly distributed between the language communities (i.e. French-speaking: 52%, Dutch-speaking: 48%) with an average of 23.7 (SD=15.5) years of practice. Prescribers characteristics are summarised in Table 1.

Table 1. Respondent characteristics

Characteristics	Total (N=152) n, (%)
Age (y), mean (SD)	52 (16)
Gender	
Women	61 (40.1)
Men	90 (59.2)
Other	1 (0.7)
User language	
Dutch	73 (48)
French	79 (52)
Region	
Brussels	40 (26.3)
Flanders	68 (44.7)
Wallonia	44 (29)
Work site	
General hospital	39 (25.7)
Psychiatric hospital	72 (47.4)
Primary care mental health service	30 (19.7)
Mobile team	12 (7.9)
Private practice	72 (47.4)
Prison	5 (3.3)
Residential facility	13 (8.6)
Other	26 (17.1)
Years of practice, mean (SD)	23.7 (15.5)
Medical resident	27 (17.8)

3.2. Psychometric characteristics and validation of the KAAPS scale

The KMO test (0.77) and the Barlett's test of sphericity ($p<0.0001$) revealed that our data were appropriate for conducting an EFA, in addition to have an appropriate sample size (i.e. 10 subjects per variable when below 200)[30]. The scree-plot suggest a 5-factors model (i.e 5 subscales). After rotation every item loaded over 0.3 with one factor and there was no cross-loading (Figure 1). All items were kept as they all have an ITC over 0.4, translating a good correlation with the other items. Internal consistency was great for the total KAAPS scale (0.89) and also good for each subscale (Table 2). Finally, the ICC of the KAAPS was above 0.7 (ICC= 0.72), indicating a good test-retest reliability.

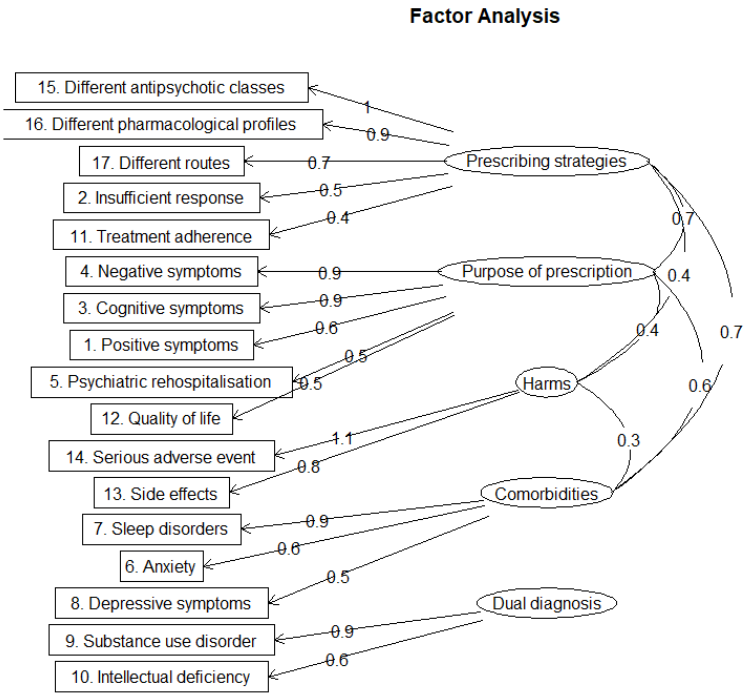

Figure 1. Diagram of the factor analysis of the KAAPS

KAAPS, Knowledge and Attitude scale toward Antipsychotic Polypharmacy in Schizophrenia

3.3. Psychiatrists' knowledge and attitude toward antipsychotic polypharmacy

The mean total score on the KAAPS scale, ranked from 0 to 102, was 55.8 (SD=13.7), and the majority of clinicians (62.5%) had a score above 51, indicating a more evidence-based knowledge and attitude.

Each response was scored on a 7-point bipolar Likert scale, and coded from 0 to 6. The most commonly known or accepted evidence for APP included "increased risk of side-effects" (4.7 ± 1.3), "increased risk of serious adverse events" (4.5 ± 1.3) and "reduced treatment-adherence" (4.3 ± 1.5). The least known or accepted evidence was that APP was inappropriate for patient with a dual diagnosis of schizophrenia and substance use disorder (2.5 ± 1.5), and for patients with a dual diagnosis of schizophrenia and intellectual disability (2.6 ± 1.6), as well as after an inadequate response to monotherapy (2.9 ±

1.4) (Table 2). The mean response regarding the use of APP for sleep disorders (3.0 ± 1.3) and the combination of different pharmacological profiles (3.0 ± 1.1) indicates that most psychiatrists are unsure with this justification for use (Table 2).

Table 2. KAAPS subscales, average response for each KAAPS item and psychometric characteristics.

KAAPS subscales and total	Mean	SD	Item-total correlation	Cronbach's α
Prescribing strategies				0.81
2.Insufficient response to monotherapy	2.9	1.4	0.67	
11.Treatment adherence	4.3	1.5	0.59	
15.Combining different classes	3.3	1.2	0.70	
16.Combining different pharmacological profiles	3.0	1.1	0.64	
17.Combining different routes of administration	3.5	1.4	0.54	
Purpose of prescription				0.83
1.Positive symptoms	3.6	1.5	0.58	
3.Cognitive symptoms	4.1	1.5	0.64	
4.Negative symptoms	4.1	1.4	0.62	
5.Psychiatric rehospitalisations	3.3	1.6	0.68	
12.Quality of life	3.4	1.6	0.72	
Harms				0.85
13.Side effects	4.7	1.3	0.41	
14.Serious adverse events	4.5	1.3	0.46	
Comorbidities				0.74
6.Anxiety	3.3	1.4	0.58	
7.Sleep disorders	3.0	1.3	0.49	
8.Depressive symptoms	3.8	1.3	0.55	
Dual diagnosis				0.77
9.Substance use disorder	2.5	1.5	0.44	
10.Intellectual deficiency	2.6	1.6	0.47	
TOTAL KAAPS				0.89

KAAPS, Knowledge and Attitude scale toward Antipsychotic Polypharmacy in Schizophrenia

3.4. Factors associated with an evidence-based attitude toward APP

Psychiatrists with higher professional social capital (β= -0.254, Standard error (SE)=0.095, p<0.01) were significantly less likely to have an evidence-based attitude toward APP, judging APP less problematic in several situations. In addition, working in a non-multidisciplinary setting (i.e. private practice, primary mental health services, prison) (β=-9.144, SE=2.395, p<0.001), belonging to the Dutch-speaking community (β=-5.133, SE=2.418, p=0.036) and prescribing a higher percentage of APP (β=-0.194, SE=0.036, p<0.001) also decreased the evidence-based attitude toward APP.

Conversely, practising cognitive behavioural therapy (CBT) (β=6.366, SE=2.411, p<0.01) increased the odds of adopting evidence-based opinions toward APP, meaning they finding APP less scientifically sounded.

Finally, the EBPAS score did not significantly explain the KAAPS score (β=0.231, SE=0.132, p=0.083) (Table 3).

Table 3. Factors associated with higher KAAPS score.

Explanatory variables	Coefficients	Standard error	P value
EBPAS	0.2307	0.1322	0.083
Professional social capital	-0.2543	0.0951	**<0.01**
Individual characteristics			
Higher percentage of APP prescription	-0.1935	0.0355	**<0.001**
Dutch speaking	-5.133	2.4182	**0.036**
Type of training in the last year			
Seminar within the institution	4.5607	2.477	0.068
Training by the pharmaceutical industry	-2.7842	2.4975	0.267
Research activity	-1.9366	2.7038	0.475
Type of journals read in the last 6 months			
French/Dutch speaking indexed journals	-2.5634	2.3807	0.284
Work setting			
Mobile team	6.9943	4.0349	0.085
Non multidisciplinary settings (Private practice, primary care mental health, prison)	-9.1435	2.3949	**<0.001**
Residential facility	-3.6112	2.4033	0.135
Type of psychotherapy			
CBT	6.3658	2.411	**<0.01**
Humanistic and family therapy	-3.0043	2.03004	0.141
Other psychotherapy	4.5796	3.41331	0.182

KAAPS, Knowledge and Attitude scale toward Antipsychotic Polypharmacy in Schizophrenia; EBPAS, Evidence-Based Practice Attitude Scale; APP, Antipsychotic Polypharmacy; CBT, Cognitive Behavioural Therapy

4. DISCUSSION

Responses to the KAAPS scale, which exhibits good psychometric properties, indicate a slight tendency of a more evidence-based attitude toward APP for the majority of psychiatrists. However, although the potential harmful effects and the propension of APP to reduce treatment-adherence were clearly acknowledged by a majority of psychiatrists, most of them still consider its use appropriate is a situation of dual diagnosis.

Up to 4.4% of patients with intellectual disability also suffer from schizophrenia, which may be explained by common genetic and environmental etiologies[35]. In patients with a diagnosis of intellectual disability only, antipsychotics are used primarily for the management of aggressive, violent or other challenging behaviour[36], thus more for their calming effects[37] than for the management of psychotic symptoms.[38,39] The use of APP in patients with a dual diagnosis of both schizophrenia and intellectual disability is likely to be justified by prescribers by the addition of one antipsychotic for the management of challenging behaviours (e.g. zuclopenthixol[40]) on top of another for the treatment of psychotic symptoms, when a single antipsychotic can be used for both indications. It is recommended to follow the schizophrenia guidelines even for patients with a dual diagnosis, and thus to avoid APP[41], especially as these patients are at increased risk of motor adverse effects.[37]

Patients with a dual diagnosis of schizophrenia and substance use disorder (SUD) are difficult to treat. This is because SUD reduces the effect of antipsychotic medication in patients with schizophrenia leading to more severe positive symptoms, reduced adherence to treatment[42], and negatively affecting the course of the illness.[43] Little is known about which antipsychotic should be use first in patients with SUD, but there is some evidence that clozapine and risperidone are more effective in reducing substance use and craving, respectively[44]. Thus, similar to patients with a dual diagnosis of schizophrenia and intellectual disability, patients with comorbid SUD may be prescribed APP as one antipsychotic is intended to treat the SUD and the other the psychotic symptoms. However, these patients should be prescribed antipsychotics following the schizophrenia guidelines, thus avoiding APP, as no evidence of any benefit of one treatment strategy over another has been demonstrated.[10,42] More generally, when there is no high-quality data in favour of a strategy, clinicians tend to find APP more acceptable.

Psychiatrists with higher professional social capital (β= -0.225, p=0.013) were significantly less likely to own an evidence-based attitude toward APP. The diffusion of innovation, and hence EBM, is more likely to occur through

interpersonal relationships rather than through the requirement of authorities[15]. However, the existence of structural holes implies that psychiatrists socialise around shared opinions leading to the most socially integrated clinicians expressing the same attitude, and therefore reduce the propensity for the penetration of new findings from outside the network[15]. Thus, higher social capital in countries where EBM prescribing or deprescribing are well-established practices within the psychiatric community tends to increase physicians propensity to adopt a positive attitude toward these practices, whereas the opposite may be true in countries where EBM prescribing and deprescribing are not yet fully accepted and remain an innovation[15]. Indeed, in the latter situation, strong cohesion may hinder the adoption of this innovation in the network, as it is perceived as coming from abstract researcher or from another culture (i.e. the culture of research)[29], which is probably what appears in our population.

Furthermore, psychiatrists working in non-multidisciplinary settings (i.e. private practice, primary mental health services, prison) were also less likely to adopt an evidence-based attitude towards APP (β=-9.338, $p<0.001$). This confirms our previous hypothesis, as similarly, psychiatrists working alone have less contact with clinicians outside the network they have built, and may be less inclined to follow innovations from other networks. On the other hand, those working in a multidisciplinary setting have a higher odd of coming into contact with innovations from other networks. In addition, working in a multidisciplinary setting is a more evidence-based practice, and psychiatrists practising in such settings are therefore more prone to adopt a position in favour of evidence-based medicine when prescribing antipsychotics for schizophrenia.

Conversely, the practice of cognitive behavioural therapy (CBT) was significantly positively associated with a more evidence-based attitude toward APP. CBT is the psychotherapy with the strongest evidence of effectiveness in the management of several mental disorders[45-47] and it is possible that psychiatrists who practice this psychotherapy are also more inclined to follow the strongest evidence when using pharmacotherapy.

Finally, having a higher EBPAS score, reflecting a more general EBM orientation, was not significantly correlated with a higher KAAPS score, although it persisted in the statistical model toward a positive association. Thus, in our population, social capital appears to have a greater influence on prescribing strategies than personal EBM orientation.

Although the KAAPS has good psychometric characteristics, and the respondents to the survey are a good representation of the Belgian population of psychiatrists (i.e. a good distribution between the regions of Belgium, the linguistic communities and the workplace), some limitations have to be taken into account for the interpretation of the results. The response rate of 12.1% may raise concerns about generalisability. However, for survey involving physicians, lower response rates are expected[48,49], due to lack of time available and it has been shown that psychiatrists have the lowest response rate of all specialists[50]. Furthermore, although financial incentives have been shown to increase the response rate of physicians[50,51], we have chosen not to use them. Nevertheless, it has been recently recognised that there is little relationship between a low response rate and biased results and that a higher response rate does not protect against biased results. It is more appropriate to compare the characteristics of non-respondents with those of respondents [52,53]. The non-respondents of this survey were similar to the respondents in their demographic characteristics (eTable 3).

5. CONCLUSION

Social capital influences attitude toward the use of antipsychotic polypharmacy in schizophrenia. Implementation strategies using the social capital of clinicians should be considered to reduce the non-EBM use of APP in schizophrenia.

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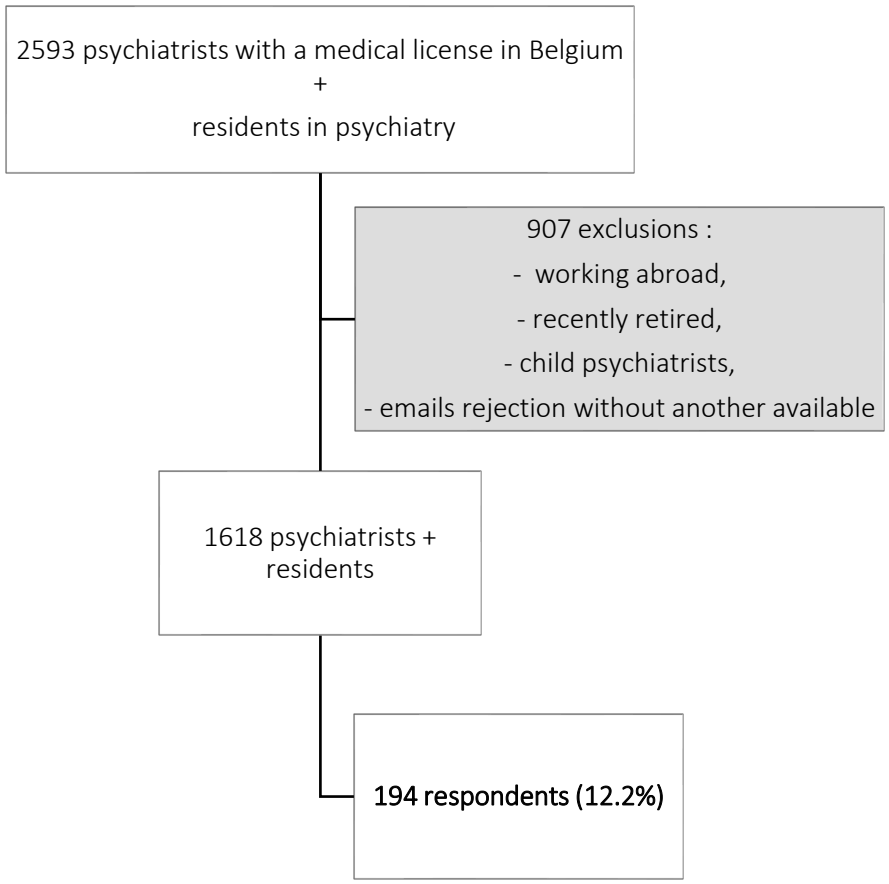
APPENDIX



eFigure 1. Flowchart of survey inclusion and response

eTable 1. List of factors tested for their potential association with the KAAPS score

EBPAS[†] score
Professional social capital with the RG-Psy[¥] total score
Age
Gender
Primary spoken language: Dutch or French
Number of years of practice
Level of seniority: resident or senior
Region of practice: Brussels, Wallonia or Flanders
University of graduation
Type of continuous education:
Seminar within the institution
Training from a pharmaceutical industry
Training from professional associations
French/Dutch speaking congresses
International English-speaking congresses
Having a research activity
Having a teaching activity
Doing scientific monitoring
Type of scientific journal read within the last 6 months:
Medical news (not indexed)
French/Dutch language scientific journals (indexed)
International English language scientific journals (indexed)
No journal
Work setting:
Hospital
Mobile team
Outpatient practice (private practice, primary mental health service, medical center, prison)
Residential facility (group homes, nursing homes, supervised residential facilities)
Type of psychotherapy practiced:
Psychoanalysis
Cognitive behavioural therapy (CBT)
Humanistic therapy or family therapy
Other
Self-estimated percentage of APP* prescribing

[†]EBPAS, Evidence-Based Practice Attitude Scale; [¥]RG-Psy, Resource Generator for Psychiatrists; *APP, Antipsychotic polypharmacy

eTable 2. Characteristics of the population of respondents and of non-respondents

Characteristics	Respondents (n=152) n, (%)	Non-respondents (n=44) n, (%)	p-value
Age (y), mean (SD)	52 (16)	47 (18.5)	0.24
Gender			0.457
Women	61 (40.1)	22 (50)	
Men	90 (59.2)	22 (50)	
Other	1 (0.7)	0	
User language			0.127
Dutch	73 (48)	27 (61.4)	
French	79 (52)	17 (38.6)	
Region			0.03
Brussels	40 (26.3)	14 (32.6)	
Flanders	68 (44.7)	25 (58.1)	
Wallonia	44 (29)	4 (9.3)	
Workplace			0.397
General hospital	39 (25.7)	9 (20.5)	
Psychiatric hospital	72 (47.4)	24 (54.6)	
Primary mental health service	30 (19.7)	8 (18.2)	
Mobile team	12 (7.9)	1 (2.3)	
Private practice	72 (47.4)	19 (43.2)	
Prison	5 (3.3)	2 (4.6)	
Residential facility	13 (8.6)	3 (6.8)	
Other	26 (17.1)	4 (9.1)	
Years of practice, mean (SD)	23.7 (15.5)	20.3 (17.8)	0.266
Medical resident	27 (17.8)	13 (29.6)	0.094

CHAPTER III

Personalised care

CHAPTER III

Impact of a caffeine restriction policy on inpatients with schizophrenia: a pre-post comparison using electronic health records

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ABSTRACT

Background/Purpose: Caffeine is the most commonly used psychostimulant worldwide. Although its large intake is suspected to worsen psychotic symptoms because of increasing dopamine neurotransmission, schizophrenic patients are heavier caffeine consumers than the general population. This study aims to assess the impact of a caffeine restriction policy in a psychiatric hospital on patient psychopathology, hospitalization characteristics, and psychotropic prescribing patterns.

Methods: It is a retrospective cross-sectional study based on electronic health records of a psychiatric hospital in the French-speaking area of Belgium. Two different periods of time were compared, the first (N=142), in 2017, when caffeine was available in the institution and the second (N=119), between Nov. 2018 and Nov. 2019 after the restriction of access to caffeine was implemented. Adult inpatients with schizophrenia or schizoaffective disorder admitted for an acute hospitalization were included. Antipsychotic exposure, benzodiazepine daily dose, GAF scores, length of hospital stay and some other factors were tested for their potential association with the decaffeinated period.

Results: After adjusting for potential confounders, reduced caffeine availability inside the hospital was significantly associated with higher GAF scores at discharge (aOR=2.86 [1.77-4.62]) and shorter hospital stays (aOR=0.68 [0.47-0.99]), but was not associated with change in antipsychotic exposure at discharge (aOR=1.04, 95% CI [0.64-1.7]) or benzodiazepine daily dose (aOR=0.89, 95% CI [0.61-1.29]).

Conclusions: Limiting access to caffeine in psychiatric hospitals is a simple and inexpensive intervention that should be promoted, especially for patients with schizophrenia.

INTRODUCTION

Caffeine, the main active substance of coffee, tea, and cola sodas, is the most widely used psychostimulant drug worldwide [1].

Although a similar proportion of the general population and the population with schizophrenia are regular caffeine consumers, caffeine intake is heavier among schizophrenic individuals [2]. Motivations evoked to underly this large use among inpatients include boredom during hospitalizations and appetence for a stimulating effect to balance the sedative properties of most psychotropic drugs [3].

The major mechanism of action of caffeine is the antagonism of adenosine receptors A_1 and $A_{2A.}$ These receptors influence glutamatergic and dopaminergic neurotransmissions, the two main systems that are affected in schizophrenia. Caffeine increases dopaminergic transmission and might worsen symptoms of schizophrenia [4].

Several cases have been reported on patients with stable schizophrenia who experienced worsening hallucinations or delusions after having increased their daily consumption of caffeine [5-8]. In a previous trial, the intake of 10 mg/kg of caffeine in stable schizophrenic patients resulted in worsening of symptoms [6]. In most cases, symptoms resolved by reducing the amount of caffeine intake without modifying the medication regimen [5,7,8]. In addition, de novo psychotic or manic symptoms have also been reported after excessive caffeine consumption in patients without any history of psychotic illness [7,9].

Impact of reducing caffeine intake on symptoms of schizophrenia has received limited attention and current evidence comes from small sample size studies [10,11]. To the best of our knowledge, no real-world observational study has never been described. Impact of caffeine reduction on the prescription of psychotropic medications, considering potential confounding factors, is unknown.

At Hôpital du Beau Vallon, a large Belgian psychiatric hospital, caffeinated sources have been replaced by decaffeinated beverages in the hospital in mid-2018. This context allows for a naturalistic evaluation of the impact of a caffeine withdrawal policy on inpatients suffering from schizophrenia or schizoaffective disorder.

The aim of this study was to investigate the evolution of patient symptoms, hospitalization characteristics and psychotropic prescribing patterns following the withdrawal of caffeine availability inside a hospital.

MATERIALS AND METHODS

It is a retrospective cross-sectional study before and after the implementation of a caffeine withdrawal policy in a psychiatric hospital.

The exposed group includes all inpatients hospitalized in 2017 and entering the inclusion criteria. The year 2017 is the last year when caffeine was still available inside the hospital. The group without caffeine includes inpatients hospitalized in the same hospital between the 1st Nov. 2018 and the 1st Nov. 2019 and meeting the inclusion criteria. Inclusion criteria are adult inpatients (i.e. 18-65 years old) with a diagnosis of schizophrenia or schizoaffective disorder (i.e. DSM-5 295.xx)[12] and admitted to the psychiatric hospital for an acute hospitalization (i.e. less than one year). If a patient was hospitalized more than once during the study period, only data from the last hospitalization were collected.

Data collected in our previous study were used for the control group (i.e. without caffeine available)[13]. Data of the exposed group (i.e. with caffeine available) were collected between January and April 2022 from electronic health records and the hospital prescribing software. The study protocol was approved by the ethics committee of the Beau Vallon hospital.

GAF scores (i.e. Global Assessment of Functioning scale) and mean length of hospital stays were tested for their potential association with caffeine withdrawal, after adjusting for potential cofactors. The GAF scale ranges from 0 to 100, and aims at evaluating the overall psychopathological state of

mentally ill patients, with 0 being the most severe and 100 the best global functioning [14]. In Belgium, psychiatrists are required to assess each patient admitted to a psychiatric unit with the GAF scale, both on admission and at discharge, making these scores available in each patient's medical record.

Prescribing patterns of antipsychotics and benzodiazepine receptor agonists (BZRAs), prevalence of patients receiving an antipsychotic "as needed" during their hospitalization, and number of antipsychotics at discharge were also tested. Antipsychotic exposure is expressed as the ratio of the prescribed daily dose (PDD) to the defined daily dose (DDD) of the World Health Organization. Antipsychotics were identified using the Anatomical Therapeutic Chemical (ATC)-group N05A, with the exclusion of lithium (ATC N05AN01). Mean BZRAs daily dose during the stay was calculated using a lorazepam equivalent dose based on the Belgian official compendium (CBIP/BCFI)[15].

Type of potential confounders considered in the model include demographic and individual factors (e.g. age, sex, smoking habits, intellectual disability), hospitalization characteristics (e.g. involuntary admission), and pharmacologic treatment (e.g. type and route of antipsychotics).

Multivariable logistic regression with multiple imputation for missing data was performed to detect factors associated with no availability of caffeine inside the hospital, in which p-values<0.05 were considered statistically significant. The statistical analyses were performed using R software version 4.0.3.

RESULTS

Sociodemographic characteristics were similar between the group of patients with available caffeine (N=142) and the group without caffeine (N=119), with a mean age of 43 (SD=12) in both groups, 31.4% (n=44) and 31.9% (n=38) of the patients living in a residential facility (p=0.082), and 56.9% (n=74) and 59.7% (n=59.7) having a legal guardian, respectively (p=0.701) (Table 1).

Table 1. Characteristics of the two populations, during the period of time with caffeine fully available and after the restriction of access to caffeine

Characteristics	Group with caffeine (N=142)		Group without caffeine (N=119)		p Value
	n	%	n	%	
Sociodemographic characteristics					
Male	9	6.3	13	10.9	0.263
Female	133	93.7	106	89.1	0.263
Age (y), mean (SD)	43	12	43	12	
Living situation					0.082
Residential facility	44	31.4	38	31.9	
Homeless	2	1.4	8	6.7	
Living alone or with relatives	94	67.2	73	61.4	
Legal guardian	74	56.9	71	59.7	0.701
Unemployed	126	90	111	93.3	0.38
Comorbidities					
Tobacco smoking	68	49.3	70	58.8	0.134
Alcohol use disorder	56	40.3	22	18.5	**<0.001**
Substance use disorder	46	32.9	26	21.8	0.053
Intellectual disability	29	20.7	18	15.1	0.262
Hospitalization characteristics					
Involuntary admission	48	33.8	29	24.4	0.104
Length of hospital stay (d), median (IQR)	42	17-95	42	18-83	0.739
GAF score admission, mean (SD)	36	13	33	12	0.107
GAF score discharge, mean (SD)	40	13	45	12	**0.005**
Primary diagnosis					0.599
Schizophrenia	102	71.8	81	68.1	
Schizoaffective disorder	40	28.2	38	31.9	

SD, standard deviation, IQR, Interquartile range, GAF, Global Assessment Functioning score. p-values <0.05, in bold, are considered significant.

After adjusting for potential confounders, reduced caffeine availability inside the hospital was significantly associated with a higher GAF score at discharge (aOR=2.86 [1.77-4.62]) even though a lower GAF score on admission was significantly associated with the group with restricted access to caffeine (aOR=0.42 [0.26-0.67]).

A shorter length of hospital stay was also significantly associated with the decaffeinated period of time (aOR=0.68 [0.47-0.99]).

However, reduced in-hospital caffeine availability was not associated with a change in antipsychotic exposure at discharge (aOR=1.04, 95% CI [0.64-1.7]) and BZRA daily dose (aOR=0.89, 95% CI [0.61-1.29]).

Removing caffeinated beverages did not reduce the odds of receiving an “as needed” antipsychotic during the stay (aOR=1.17 [0.46-2.97]) or change the number of antipsychotics per patient at discharge (aOR=0.67 [0.36-1.24]) (Table 2).

Table 2. Factors associated with reduced caffeine availability inside the psychiatric hospital in patients with schizophrenia, in a multivariable regression model

Variables	aOR	95% CI	p Value
Patients characteristics			
Age	0.82	0.5-1.33	0.415
Female	0.38	0.12-1.15	0.087
Tobacco smoking	2.87	1.44-5.72	**0.003**
Alcohol use disorder	0.22	0.10-0.47	**<0.001**
Substance use disorder	0.5	0.22-1.15	0.101
Intellectual disability	0.77	0.33-1.79	0.544
Unemployed	2.02	0.69-5.97	0.202
Legal guardian	1.18	0.6-2.32	0.638
Homeless	9.36	1.42-61.58	**0.02**
Antipsychotic treatment			
Antipsychotic exposure[†] at discharge	1.04	0.64-1.7	0.863
At least one LAI at discharge	2.32	1.22-4.42	**0.01**
At least one FGA at discharge	1.57	0.69-3.55	0.279
As needed antipsychotic during the stay	1.17	0.46-2.97	0.742
Number of antipsychotics at discharge	0.67	0.36-1.24	0.202
Hospitalization			
Involuntary admission	0.47	0.23-0.97	**0.04**
GAF score admission	0.42	0.26-0.67	**<0.001**
GAF score discharge	2.86	1.77-4.62	**<0.001**
Length of hospitalization	0.68	0.47-0.99	**0.045**
Co-treatment			
Daily dose of BZRAs	0.89	0.61-1.29	0.53
Diagnosis			
Schizoaffective disorder	1.27	0.66-2.46	0.479

aOR, Adjusted Odds Ratio, LAI, Long-acting injectable antipsychotic(s), FGA, First Generation Antipsychotic(s); GAF, Global Assessment of Functioning scale; BZRAs, Benzodiazepine Receptor Agonists.

[†]Antipsychotic exposure is expressed as the ratio of the prescribed daily dose (PDD) to the defined daily dose (DDD) of the World Health Organisation.

p-values <0.05, in bold, are considered significant.

DISCUSSION

After adjusting for potential confounding factors, a higher GAF score at discharge, reflecting a better psychopathological state of patients, was significantly associated with the decaffeinated period. As this group was also significantly associated with a lower GAF score on admission, it reflects an even greater improvement in GAF scores over the course of hospitalizations in the decaffeinated group than in the caffeinated one. It confirms previous findings of improvement in symptoms of schizophrenia by reducing access to caffeine in a hospital [10,11].

In addition, a shorter duration of hospitalization was also associated with the period of restricted access to caffeine, indicating that patients tend to show a more rapid symptoms improvement when caffeine is not readily available in the hospital facility.

However, implementation of the decaffeinated beverage policy did not lead to a reduction in antipsychotic exposure at discharge. This finding is surprising, knowing that caffeine consumption is suspected to worsen symptoms of schizophrenia and that switching to decaffeinated beverages reduces psychotic symptoms [6,10,11]. Different hypotheses can be made. First, antipsychotics are seldomly deprescribed during a hospital stay, as we have previously shown, and antipsychotic drug regimens at discharge might thus not thoroughly translate patients' symptoms severity [13]. Second, our methodology differed from previously published studies, which were interventional trials aimed at testing symptom changes with detailed scales (e.g. BPRS). Only one study also monitored prescribing patterns by recording changes in the number of "as needed" antipsychotics and anxiolytics. This study did not find any reduction in the use of psychotropic medication after caffeine withdrawal, although it did show a diminution of psychotic symptoms [11]. This finding confirms the existence of a gap between symptom modification and re-evaluation of prescribing patterns. Finally, our setting was different from the above-mentioned trials. Indeed, one study was conducted in a closed ward only, where no supply of caffeine coming from

outside could occur, whereas our study included both open and closed wards [10]. Assuming that only high quantities of caffeine can change the severity of symptoms sufficiently to result in a revision of the daily dose of antipsychotics at discontinuation, and that heavy consumers presumably find their way to caffeinated beverages even when not available in the hospital, this may have overshadowed the effect [2].

Exposure to BZRA during the stay was also not significantly reduced by the new decaffeination policy. As caffeine has an anxiogenic effect, the administration of anxiolytics was expected to be lowered by its eviction [16]. However, acutely admitted patients with schizophrenia are often agitated and require sedative medications such as short-term benzodiazepines [17]. The effect of caffeine withdrawal on anxiety might therefore be more visible in stable patients without acute exacerbations.

Potential limitations may be considered for the interpretation of these findings. Daily caffeine intake could not be monitored, as caffeine plasma concentrations are not routinely measured. However, it has been previously demonstrated that restricting access to caffeine inside a hospital lessened the daily intake of patients [11]. In addition, it cannot be excluded that shorter hospital stays are the result of a new healthcare policy, but the two time periods were chosen very close to each other to avoid a possible bias induced by a change in hospital policy. Finally, although caffeine is a potential competitive inhibitor of CYP1A2, the effect of caffeine withdrawal on plasma concentrations of antipsychotics could not be quantified due to lack of availability. Indeed, in Belgium, therapeutic drug monitoring (TDM) of antipsychotics is not performed in clinical routine. However, only clozapine and olanzapine are primary metabolized by the CYP1A2 [18], which does not affect the pharmacokinetics of all other antipsychotics investigated. Furthermore, removal of this potential drug-drug interaction would have lifted the inhibition, which could have lowered the plasma concentration of clozapine and olanzapine [19] and, if clinically significant, resulted in worsening of patients' symptoms. Despite this, as higher GAF scores were significantly associated with the decaffeinated period, this reflects a potentially even

stronger pharmacodynamic effect of caffeine suppression on patients with schizophrenia, and further supports our results.

In conclusion, improvement in the psychopathological state of patients and reduction of the length of hospitalization supports the limitation of caffeine availability inside psychiatric hospitals, especially for patients suffering from schizophrenia spectrum disorders.

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AntiPSYCHotics' Individualized Care : understanding clinical response in relation to plasma concentrations and genetic variability

DESCRIPTION OF THE PSYCHIC TRIAL AND PRELIMINARY RESULTS

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1. BACKGROUND

Schizophrenia is a mental illness that affects about 1% of the world population[1].

Antipsychotics are the cornerstone of schizophrenia and schizoaffective disorders treatment [1]. However, about 30% of schizophrenia patients had no or minimal symptomatic improvement after 2 antipsychotic's trials at an appropriate dosage and duration, and are referred to as treatment-resistant schizophrenia (TRS) patients[2-4]. TRS is an everyday challenge for psychiatrists and caregivers, and these patients cost approximatively 3 to 11-fold more than good responders because of increased use of health care resources[5]. However, about one third of patients identified as TRS by their psychiatrist has undetectable antipsychotic plasma concentrations and another third has subtherapeutic ones[6,7]. The data from our first study[8] show that, in clinical routine, plasma levels are seldomly measured.

Subtherapeutic plasma levels of antipsychotics can be explained by a poor adherence and/or pharmacokinetic variabilities through genetic factors and drug-drug/food-drug interactions, increasing the risk of a non-response [9-12]. Conversely, patients with supratherapeutic plasma concentrations are more susceptible to experience adverse effects, making them at higher risk of spontaneous treatment-discontinuation[10]. Aripiprazole, olanzapine, and risperidone are the most frequently prescribed atypical antipsychotics in Belgium for the treatment of schizophrenia that are metabolized, according to our retrospective data[8]. They are substrate of CYP2D6, CYP3A4/5 and/or CYP1A2 as well as ABCB1. *CYP450* and *ABCB1* polymorphisms impact plasma levels of antipsychotics, the most robust evidence being *CYP2D6* polymorphism on aripiprazole and risperidone concentrations[12,13]. However, the consequences of these pharmacogenetic associations with pharmacokinetics on antipsychotics' response and/or tolerance are less evident and have been less extensively explored [11,13]. Besides, most of the existing studies focused on one or two genes solely and as most of them are based on a retrospective design, lacked of a complete overview on factors

that can potentially explain the therapeutic response diversity in an everyday practice [14].

Studies investigating the impact of a panel of pharmacogenes and their correlation with pharmacokinetic variabilities but foremost, the clinical impact in a real-life setting are thus missing. Practically, clinicians faced lack of actionable messages because of the absence of reliable clinical evidences.

The aim of this study was to detect the impact of several factors (i.e. genetic polymorphism, drug-drug interactions, smoking) on pharmacokinetics of three atypical antipsychotics in a population suffering from schizophrenia spectrum disorders. Clinical outcomes were also measured in order to distinguish a real treatment-resistant schizophrenia from a suboptimal treatment.

The primary outcome was the correlation between plasma concentrations of each antipsychotic and genetic polymorphism, considering environmental factors (e.g. drug-drug interactions, smoking).

The secondary outcome was the correlation between clinical response, plasma concentrations of each antipsychotic and genetic polymorphism of a panel of pharmacogenes, considering environmental factors (e.g. drug-drug interactions, smoking).

2. METHODS

2.1. Design

It is a prospective multicentric study taking place in 7 Belgian hospitals.

This study has a naturalistic design, meaning that the investigators interfered as little as possible with the real-life activities and treatment during patients' hospital stays. The medicines were prescribed as the standard of care.

The interventions were one additional blood sample at steady state of the studied antipsychotic, one questionnaire on side effects (i.e. UKU-patient) and one CGI score every week (maximum 3 CGI-I).

2.2. Inclusion criteria

Inclusion criteria are : (1) diagnosis of schizophrenia-spectrum disorders[1] (DSM-V 295.xx, 298.9 and 297.1 ; or ICD-10 F20.xx, F25.xx, F29 and F22; or ICD-11 6A20, 6A21, 6A2Z and 6A24), (2) hospitalised in a psychiatric unit of each centre for an acute episode of psychosis, (3) aged between 18 and 65 years old at admission; and (4) taking a monotherapy[2] of aripiprazole, olanzapine or risperidone at admission or any time during their hospital stay for their psychotic symptoms until steady state of their antipsychotic is reached. Diagnosis will be confirmed by a senior psychiatrist in each centre (i.e. the local investigator), according to the DSM-5 criteria.

2.3. Exclusion criteria

Exclusion criteria are: (1) comorbid disorder of intellectual development (i.e. intellectual disability, DSM-5 criteria 317.xx and 318.xx), (2) comorbid serious uncontrolled illness or dementia[3]; (3) comorbid substance use disorder (DSM-V 305.20, 304.30, 305.90, 304.60, 305.30, 304.50, 305.50, 304.00, 305.40, 304.10, 305.70, 305.60, 304.40, 304.20) in case of consumption during the hospital stay[4] (4) comorbid alcohol use disorder (DSM-V 305.00 and 303.90); (5) women with a current pregnancy[5] ; (6) hospitalization for a

[1] Schizophrenia, schizoaffective disorders, delusional disorders, psychosis no otherwise specified (NOS)

[2] A cotreatment with prothipendyl ≤80mg (e.g. for insomnia), and quetiapine ≤300 mg (e.g. for depressive symptoms) will be considered as monotherapy as not reaching the therapeutic plasma concentration for psychosis.

[3] These patients will be excluded because of potential worsening of symptoms independently of the antipsychotic, or because assessment would be bias by the condition. Serious uncontrolled illness will be determined by each local investigator.

[4] In case of suspicion of consumption, a urine drug screen could be performed according to routine care

[5] These patients will be excluded because of modification of pharmacokinetics, and because exacerbation of symptoms can be caused by the pregnancy, causing a bias.

social purpose (e.g. nursing home time out) or planned hospitalisation without exacerbation ; (7) patients not speaking French, English or Dutch to a standard necessary to receive the assessment scales; (8) patients with an hepatic fibrosis Child Pugh C and severe renal failure (i.e. Clcr <30 mL/min) identified through chart review.

2.4. Efficacy and tolerance criteria

Clinical response of the patient was assessed by the treating psychiatrist using the Clinical Global Impression (CGI) scale (see Appendix 1)[15]: (1) CGI-Severity (CGI-S) at baseline (i.e. hospital admission); (2) CGI-Improvement (CGI-I) every week until 3 CGI-I have been completed after the introduction of the studied antipsychotic, switch to another antipsychotic or discharge. In case of discharge or switch to another antipsychotic before week 3, the last CGI was used in a strategy of the last-observation-carried-forward. A CGI score of 4 ("no change") or more (i.e. 5 "minimally worse", 6 "much worse", 7 "very much worse") is considered as an absence of clinical response to the antipsychotic.

Tolerance was evaluated using the UKU-patient self-rating scale (see Appendix 2), which is a version adapted from the UKU-scale and specifically designed to be completed by the patient himself[16,17]. This scale encompasses 40 questions on symptoms with 5 additional questions exclusively for women and 3 exclusively for men. Each response is given as a 4-points Likert scale (i.e. from 0 to 3). As the total number of questions are different for women and men, a sum of the ratings of the items shared by both women and men was calculated to measure the total shared score. As the 4-points Likert scale ranges from 0 to 3, the maximum total shared score is 120. Then another score with all the items for women (i.e. maximum 135) and for men (i.e. maximum 129) was calculated, and reduced to 100 to allow comparison. The UKU-patient scale was filled once the target dosage or maximum tolerated dose of the studied antipsychotic is reached. As patients suffering from schizophrenia may have impaired cognitive functions, the questionnaire was filled with the help of the coordinating investigator (JL). Finally, the

consequences of the side effects were also be recorded: (1) no consequence, (2) reduced dosage or treatment added to correct the side effect, (3) switch to another drug.

2.5. Recruitment modalities

The coordinating investigator (JL) screened patients for inclusion once a week and/or the local investigators of each hospital involved let the coordinating investigator knows if a patient would enter the inclusion criteria. When the coordinating investigator identified a patient entering the inclusion criteria, an interview with the patient was planned. The study was then presented to the patient, and if the patient was able to consent according to his psychiatrist or local investigator and willing to participate, he/she was asked to give a written informed consent. When necessary (i.e. the psychiatrist doubts the patient's ability to consent), the Mac Arthur Competence Assessment Tool for Clinical Research (Appendix 3) could be performed to confirm the patient's ability to consent.

2.6. Baseline characteristics

The following characteristics were collected at the time of inclusion: Age, sex, living situation (i.e. living alone, homeless, living in a nursing facility), age of illness'onset, type of hospital admission (i.e. voluntary or involuntary), smoking habits (i.e. number of cigarettes a day), caffeine intake, weight, comorbidities, medication scheme at the time of inclusion and at the time of the blood sample.

2.7. Subject withdrawal

Patients were withdrawn from the trial in the following situations: 1) At hospital discharge; 2) When 3 CGI-I have been completed, the UKU filled and the blood sample withdrawn, even if the patient was still hospitalized 3) When a discontinuation criterion was met.

2.8. Determination of antipsychotic plasma concentrations

Plasma samples were taken during hospitalisation, at steady state of each antipsychotic, with no strong inhibitors or inducers of CYP450 introduced

within these days. Sampling was performed by a member of the nursing staff of each centre before the next intake to measure trough concentrations. Time and date of the last intake of the studied antipsychotic and of sampling were recorded by the nurse in charge of the patient. Samples were collected by the coordinating investigator, and stored at -20°C at the UCLouvain after centrifugation, until analysis.

Antipsychotics' plasma concentrations were determined by LC-MS-MS regularly during the study period, after sufficient number of samples have been collected, allowing a batch analysis. Each run will include a quality control sample to ensure no batch effect. Samples were analysed at the CUSL laboratory.

2.9. Determination of patients' genotypes

An additional blood sample was taken for DNA extraction to determine the genotype of each patient. Samples were collected by the coordinating investigator and stored at +4°C. Genetic testing were performed as a batch analysis using a validated Next Generation Sequencing (NGS) panel developed by Pr V. Haufroid (Louvain Center for Toxicology and Applied Pharmacology, LTAP, UCLouvain, Brussels, Belgium).

3. STATISTICAL ANALYSIS

The statistical analysis was performed using R software. The plasma concentrations were dose-adjusted (concentration/dose ratio). The correlation between dose-adjusted plasma concentrations and different SNPs and covariates (e.g. cotreatment, age, baseline weight, sex, smoking) were tested using a linear regression. The association between treatment response (i.e. CGI-I scores) and side effects (i.e. UKU-patient scores) with the plasma concentrations, SNPs and covariates (e.g. cotreatment, age, baseline weight, sex, smoking) were assessed using a linear regression.

4. ETHICS ASPECT AND INFORMED CONSENT

The protocol of this multicentric study was submitted to a central Ethics Committee providing the central opinion for Belgium: Comité d'Ethique

Hospitalo-facultaire Saint-Luc UCLouvain. In addition, the protocol was submitted simultaneously to every local Ethics Committees of each centre involved. The protocol was submitted to the federal agency (AFMPS/FAMHP) simultaneously to the Ethics Committees.

Patients, or their legally acceptable representative (i.e. for patients not able to consent to study participation at the time of inclusion) provided written informed consent after having been fully informed about the nature and objectives of the trial.

5. CONFLICT OF INTEREST

The authors declare no conflict of interest.

6. PRELIMINARY RESULTS AND DISCUSSION

A total of 15 patients were included and completed the trial, 26.7% were women (n=4) and 73.3% were smokers (n=11) (Table 1). All included patients were on olanzapine, with a daily dose ranging from 10 to 30 mg a day.

Table 1. Participant characteristics

Characteristics	Total (N=15) n (%)
Age (y), mean (sd)	34 (11)
Female	4 (26.7)
Male	11 (73.3)
Living situation	
Alone or with relatives	13 (86.7)
Homeless	1 (6.7)
Residential facility	1 (6.7)
Involontary admission	12 (80)
Smoker	11 (73.3)
Antipsychotic Olanzapine	 15 (100)

- Difficulty recruiting in clinical daily practice

Despite the participation of seven Belgian hospitals, only 15 patients were included in 18 months. This can be attributed to a combination of factors. First, the coordinating investigator (JL) was only authorised to carry out screening in three of the seven hospitals. In the other centres, screening was carried out either by psychiatrists or by nurses, who informed the coordinating investigator when a patient met the inclusion criteria. In all the centres where the coordinating investigator did not perform screening, no patients were included, except one. This patient was included in a centre where the coordinating investigator called the nurse in charge of the unit once a week, which was a proactive reminder to screen. However, it was not possible to ascertain whether any other patients met the inclusion criteria or whether the criteria were not fully understood, as only one patient met the inclusion criteria in 18 months.

Other factors that limited patient inclusion were: (1) patients being on antipsychotic polypharmacy, (2) switching to another antipsychotic or adding a second antipsychotic shortly after admission, before olanzapine steady state was reached, (3) uneven daily dose (e.g. 5mg in the morning, 10mg in the evening), (4) comorbid substance use disorders and (5) language barrier. The acceptance rate for patient participation was approximately 45%, which was as expected.

- Factors affecting the plasma concentration of olanzapine

Due to the small number of patients, a univariate analysis was performed on the plasma concentration on dose ratio (i.e. C/D). Three patients were excluded from the subsequent analysis because their genetic status was still unknown at the time of writing. None of the factors reached statistical significance, but certain trends emerged, most of which are consistent with previously published data.

Male patients tended to have lower olanzapine C/D (β=-1.11, Standard error (SD)=0.83, p=0.21), which is consistent with the known inhibitory effect of oestrogens on CYP1A2[18] (Table 2). It is also consistent with the literature

showing that women tend to have a 10% higher plasma concentration of olanzapine than men[19].

Smoking (β=-1.45, SD=0.69, p=0.06) and caffeine use (β=-1.41, SD=0.7, p=0.06) were also associated with lower C/D, although this was not statistically significant.

Regarding genetic polymorphism of enzymes involved in olanzapine metabolism, carriers of *UGT1A4 c.868-10021* T tended to have lower C/D (Table 2). Conversely, *UGT1A4 c.868-7110* TT individuals tended to have higher C/D (β=1.26, SD=1.16, p=0.3). This was only apparent for homozygous carriers, as heterozygous T carriers did not show any difference in C/D (β=0.38, SD=0.86, p=0.671). To our knowledge, impact of this variant on olanzapine plasma concentration or treatment response has never been reported previously.

Regarding *CYP1A2*, rs762551 AA (*1F/*1F) patient carriers had a slight tendency toward lower olanzapine C/D (β=-1.09, SD=1.44, p=0.47).

Interestingly, CYP2D6 ultra-rapid metabolisers had significantly higher C/D (β=-2.42, SD=0.97, p=0.04). This counterintuitive association could probably be explained by the fact that the two UM patients were also *UGT1A4 c.868-10021 GG*, which seems to be associated with a higher C/D of olanzapine, as previously discussed (table 2), especially since UGT1A4 is the primary metabolising pathway of olanzapine. In addition, these two patients had elevated plasma concentrations (patient 3, daily dose=20 mg, c=66,61 ng/mL, C/D=3,33; patient 6, daily dose = 15 mg; c=84.17 ng/mL and C/D=5.61), the patient 6 even being outside the therapeutic range (c=20-80 ng/mL). Aside, the fact that patient 6 was *CYP1A2*1F/*1F* did not seem to impact on olanzapine plasma concentration, which was above the therapeutic range, whereas the *CYP1A2*1F* allele is supposed to be associated with higher drug metabolism. As this patient was a non-smoker, this supports the theory that *CYP1A2*1F* codes for higher inducibility rather than higher activity[20,21]. Moreover, this patient was only receiving lorazepam as co-treatment. This suggests that in non-smokers, olanzapine variability better correlates with the *UGT1A4* than with the *CYP1A2* polymorphisms.

Table 2. Univariate analysis of the ratio of olanzapine plasma concentration on daily dose

Characteristics	Coefficient	Standard error	P value
Male	-1.11	0.83	0.21
Voluntary admission	1.57	0.75	0.06
Smoking	-1.45	0.69	0.06
Caffeine	-1.41	0.7	0.07
Weight	-0.02	0.01	0.16
UGT1A4 c.868-10021 TT	-1.54	1.43	0.31
UGT1A4 c.868-10021 TG	-0.79	0.79	0.35
UGT1A4 c.868-7110 TT	1.26	1.16	0.3
CYP1A2 rs762551 CC (*1/*1) or CYP1A2 rs762551 CA (*1/*1F)	0.75	0.79	0.36
CYP1A2 rs762551 AA (*1F/*1F)	-1.09	1.44	0.47
CYP2D6 UM	2.42	0.97	0.04

UM: Ultra-rapid metabolisers

- Factors affecting the CGI score

CGI-I scores of the included patients ranged from 1 (i.e. very much improved since the initiation of the treatment) to 4 (i.e. no change). Only two genetic variants appeared to have an impact on the response to olanzapine in our patients, although they did not reach statistical significance. Patients with *DRD2* rs6275 GG tended to have a lower CGI-I score at 3 weeks (β=-1.33, SD=0.87, p=0.158), signifying a better early response. To our knowledge, no previous data have been published on the impact of this variant on response to olanzapine, but one study showed that T carriers treated with olanzapine had higher prolactin levels[22]. This SNP, located in exon 7 of *DRD2*, results in altered mRNA folding, reduced mRNA stability and hence protein synthesis,

which is thought to reduce DRD2 up-regulation and receptor expression[23]. This could support the hypothesis of a better response to antipsychotics. Conversely, *DRD2* rs1076560 CC tended to have a higher CGI-I, meaning a lower early response (β=0.9, SD=0.73, p=0.246) (Table 3). The same effect was seen in another study where *DRD2* rs1076560 AA and AC had better response to olanzapine[24]. This SNP in intron 6 of *DRD2* affects the alternative splicing of exon 6, which significantly reduces the expression of the DRD2-short (i.e. a subtype of DRD2)[25].Other genetic variants and the C/D did not appear to have an impact on response, probably because although *CYP1A2* and *UGT1A4* polymorphisms seem to impact olanzapine plasma concentration, this may not translate into a response if plasma concentrations remain within the therapeutic range. For example, one patient whose plasma concentration was below the therapeutic range (c=12.24 ng/mL) had the worst CGI of the 15 patients (i.e. CGI-I=4, meaning no change in symptoms compared to admission).

Table 3. Factors associated with CGI-I score at weeks after olanzapine start

Characteristics	Coeff	Std error	P value
Plasma concentration/dose	-0.02	0.24	0.927
Living in a residential facility	-1.9	0.92	0.069
Involontary admission	-0.56	0.65	0.414
DRD2 rs6275 GG	-1.33	0.87	0.158
DRD2 rs1076560 CC	0.9	0.73	0.246

- Factors affecting the UKU score

UKU scores of the included patients ranged from 8 to 34. In terms of olanzapine adverse effects, a higher C/D appeared to slightly increase the UKU side effect score (β=1.36, SD=1.73, p=0.449)(Table 4). This was not statistically significant, perhaps because once the plasma concentration remains within the therapeutic range, side effect rates remain similar between individuals. However, one patient had a plasma concentration

above the therapeutic range (c=84.17 ng/mL) and had more heart palpitations, to the extent that he was treated with 1.25 mg bisoprolol per day.

A higher age was strongly associated with a greater score of side effects (β= 0.58, SD=0.13, p=0.001) which is consistent with the fact that older patients are more sensitive to effects such as anticholinergic effects, as olanzapine has strong anticholinergic properties.

Conversely, smoking seemed to slightly reduce the burden of side effects (β=-3.5, SD=4.53, p=0.457) probably by inducing CYP1A2 and lowering the olanzapine plasma concentration.

Two genetic variants were significantly associated with higher side effects burden. Patients who were *CYP2C8*3/*3* had significantly higher UKU scores (β=22.67, SD=5.2, p=0.002). No previous data have been published regarding the impact of *CYP2C8* variants on response to olanzapine, but *CYP2C8*3* carriers are known to have low ibuprofen clearance[26] and one study reported a higher C/D of tacrolimus in *CYP2C8*3* carriers[27]. This may indicate a decrease in CYP2C8 activity or expression in patients with *CYP2C8*3*, putting patients at risk of side effects.

Finally, patients being *CYP1A2* rs762551 CC (CYP1A2*1/*1) had a higher UKU score (β=19.13, SD=4.87, p=0.004), consistent with the known non-inducibility of *CYP1A2*1*. Indeed, these patients are likely to have a higher olanzapine plasma concentration, even if they are smokers.

Table 4. Factors associated with UKU adverse effect score

Characteristics	Coefficient	Standard error	P value
Plasma concentration/dose	1.36	1.73	0.449
Age	0.58	0.13	0.001
Smoking	-3.5	4.53	0.457
CYP2C8*3/*3	22.67	5.2	0.002
CYP1A2 rs762551 CC	19.13	4.87	0.004

- Preliminary conclusion

In conclusion, this study highlights the difficulty of recruiting patients with schizophrenia in daily clinical care, but also that *UGT1A4* and *CYP1A2* polymorphisms appear to impact the plasma concentration of olanzapine. This variation in plasma concentration does not seem to have an impact on efficacy (i.e. CGI-I score) as long as it remains within the therapeutic range, whereas *DRD2* polymorphism does. Moreover, side effects were greater in patients with plasma concentrations above the therapeutic range, which may also be correlated with *CYP1A2* polymorphism. Other polymorphisms of enzymes involved in minor metabolic pathways of olanzapine, such as CYP2D6 or CYP3A4, do not appear to impact its plasma concentration. However, these interpretations are based on a univariate analysis of a sample of 12 patients, and should be used with caution, but a parallel comparison with the literature has helped interpretation.

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DISCUSSION

1. OVERVIEW OF THE PROJECT AND KEY FINDINGS

Antipsychotics remain the only registered treatment of schizophrenia since their approval. The combination of at least two different antipsychotics, known as antipsychotic polypharmacy, is common practice despite the lack of evidence of superior efficacy to antipsychotic monotherapy, and even worse outcomes.

In this context, we carried out a multidisciplinary project with the aim of providing insight on the ways of improving individual pharmacotherapy with antipsychotics in patients suffering from schizophrenia.

In chapter I, we first conducted a retrospective observational study on 6 Belgian hospitals to explore the prevalence of antipsychotic polypharmacy and its evolution on admission and at discharge, as well as the characteristics associated with this polypharmacy. We also examined clozapine prescribing patterns. The study revealed that about half of patients admitted to hospital with acute decompensation of schizophrenia were on antipsychotic polypharmacy, and that this proportion even increased at discharge to about 60%. We found that patients with factors reflecting severity of the illness, such as previous clozapine use or institutionalisation, or the presence of a comorbid sleep disorder, such as total daily dose of hypno-sedatives, had an increased likelihood of receiving antipsychotic polypharmacy. In contrast, involuntary admission, alcohol use disorder and older age were among the factors reducing the odds of being prescribed antipsychotic polypharmacy. We also found that about 10% of the patients were taking clozapine, while a third were eligible. This highlights the elevated recourse to antipsychotic polypharmacy in the treatment of schizophrenia in Belgium, and the insufficient prescribing of clozapine, the only treatment registered for treatment-resistant schizophrenia. This also suggests that antipsychotic polypharmacy is used instead of clozapine in situations of poor response to treatment.

In the second part chapter I, we conducted a second retrospective observational study, using data from the first study and comparing it with data from a hospital in Montreal, Québec, Canada. The aim of this study was to determine the factors associated with antipsychotic deprescribing, that is the reduction in the number of antipsychotics, after psychiatric hospitalisation, as well as comparing psychotropic prescribing patterns on admission and at discharge in several Belgian hospitals and in the Québec hospital. We showed that patients admitted to the Canadian hospital were more likely to be described than those admitted to the Belgian hospitals. We also found additional factors associated with an increased likelihood of deprescribing such as having antipsychotic side effects. This study draws attention to the fact that antipsychotic deprescribing is already performed in identifiable patients and cultural contexts, and is therefore feasible. Strategies such as advertising Canadian deprescribing algorithms or having on-ward clinical pharmacists could be applied to increase the rate of deprescribing and reduce the prevalence of patients on antipsychotic polypharmacy.

In chapter II, we conducted a survey to better understand psychiatrists' opinions toward the use of antipsychotic polypharmacy in schizophrenia. For the purposes of this survey, we first designed and validated a scale aiming at measuring the social capital of psychiatrists (i.e. the support an individual can access through their relationships and the strength of the link by which it is accessed). This scale, called the Resource Generator for Psychiatrists (RG-Psy) has been successfully developed and validated, and has good psychometric characteristics. The survey of Belgian psychiatrists revealed that psychiatrists with lower social capital were more likely to adopt a more evidence-based attitude toward antipsychotic polypharmacy, but that their intrinsic evidence-based orientation did not influence their opinions toward this practice. This survey showed that, based on the theory of normative pressure and structural holes, the information that circulates most among highly socialised psychiatrists was still in favour of antipsychotic polypharmacy. This

suggests that deprescribing and the use of antipsychotic monotherapy remains an innovation that will have difficulty penetrating dense networks because it is perceived as coming from another network, such as the scientific community.

In chapter III, we investigated factors that can lead to poor response to treatment, or to an increase in adverse effects eventually leading to poor adherence, that may subsequently result in recourse to antipsychotic polypharmacy.

At the Beau Vallon Hospital, a large Belgian psychiatric hospital, caffeine beverages were replaced by decaffeinated drinks in mid-2018. In a retrospective cross-sectional study, we investigated the effect of withdrawing the availability of caffeine on patient outcomes. We found that reducing access to caffeine within the hospital was associated with better patient functioning and shorter hospital stays, but that this did not translate into a change in the daily dose of antipsychotics or benzodiazepines.

Finally, we conducted a multi-site clinical trial, the PSYCHIC trial, with 7 hospitals included, to better understand the impact of genetic polymorphism on the plasma concentration of olanzapine, the most frequently prescribed antipsychotic in Belgium, as well as the impact of both pharmacogenetics and plasma concentration on patient outcomes. This study highlighted the difficulty of carrying out therapeutic drug monitoring (TDM) and pharmacogenetic testing in daily psychiatric clinical practice. After 18 months, only 15 patients had been included. We identified a number of reasons that may contribute to impediments to this practice, such as insufficient knowledge on the timing of blood sampling required to measure steady-state plasma concentration, and lack of locally available laboratories. Other obstacles include the unevenly distributed olanzapine regimen (e.g. 5 mg in the morning, 10 mg in the evening), which complicates the interpretation of the TDM, or recourse to antipsychotic polypharmacy a few days after starting olanzapine, which makes it impossible to measure the

effect of olanzapine alone. The presence of a clinical pharmacist was mandatory to ensure an appropriate drug regimen and sampling for proper interpretation of the TDM and pharmacogenetic tests.

2. CRITICAL APPRAISAL

2.1. INPUT OF THIS PROJECT

Since the 1970s, modern medicine has moved from prescribing decisions based on clinicians' experience to shared decision-making between patient and clinician based on the best available evidence, known as evidence-based medicine[1]. However, since then, still up to 40% of patients receive care that is not based on current scientific evidence, and about 25% receive unneeded or harmful treatment[2]. Physicians in the psychiatric field are even the least likely to report adoption of evidence-based medicine compared with other fields of medicine, which may be due to the fact that psychiatry benefited from high quality evidence later than other medical specialties[1]. In Belgium, little was known about the quality of pharmacotherapy administered to patients with schizophrenia, especially with regard to the use of antipsychotic polypharmacy (APP), which appears to be a widespread practice worldwide. In addition to not benefiting patients, APP worsens patient outcomes and functioning, reducing the possibility of achieving remission and recovery.

For that reason, throughout this thesis, we have attempted to measure the extent of the use of antipsychotic polypharmacy and other prescribing practices (e.g. the use of clozapine for treatment resistance) in schizophrenia. We included 6 Belgian hospitals, and were able to show that improvements are still needed, as more than half of individuals with schizophrenia are discharged with antipsychotic polypharmacy after psychiatric hospitalisation. Our pharmacoepidemiology study is important to raise awareness of the need for more careful prescribing in this population, and to help develop targeted interventions for patients most likely to be prescribed antipsychotic polypharmacy. In addition, the comparison with a hospital based in Québec, where practices are more evidence-based, helps to show that antipsychotic

deprescribing is feasible, as is already done naturally (without specific intervention) in other countries, which may help to overcome the barrier of outcome expectancy. This may also help to develop interventions or instigate changes in practices inspired by those in Québec.

The survey enabled us to gain a better understanding of psychiatrists' opinions on antipsychotic polypharmacy. This was essential, as little was known about psychiatrists'attitude to this prescribing practice. Awareness of their views will help in developing educational materials or other interventions, by knowing in which situations APP is most likely to be considered justified. As our survey has shown that social capital influences attitude toward APP, it will be possible to recourse to key opinion leaders to improve the uptake of the latest evidence into clinical practice.

Finally, understanding the factors that lead to poor response, and therefore to the use of polypharmacy or other suboptimal treatments, is a step toward better prescribing. Showing that withdrawal of caffeine improves patient functioning and shortens hospital stay is useful as this measure is inexpensive and simple to implement and could therefore be easily applied at a national level. Finally, using therapeutic drug monitoring and pharmacogenetics in psychiatry to guide prescribing would help to find the most effective dose by detecting interindividual variabilities in drug metabolism. This would ultimately lead to improved patient outcomes, and therefore reduce suboptimal prescribing. Conducting a multisite clinical trial has also raised awareness among healthcare professionals of pharmacogenetics and therapeutic drug monitoring and their relationship to treatment response. This could lead to greater use of these techniques in clinical routine to understand poor response or high side effect burden, thereby reducing the use of APP. This trial also detects barriers to therapeutic drug monitoring and pharmacogenetic testing in routine clinical practice in psychiatric hospitals, barriers that should be considered in depth if these tests are to be used more widely.

2.2. STRENGTHS

RESEARCH METHODS

- The pharmacoepidemiology studies

Pharmacoepidemiology is the study of drug use, drug effects and effects of efforts or policies to improve the use of medicines in populations[3]. The two main databases used for such studies are medical records databases or administrative databases. Our pharmacoepidemiology studies have used medical records, which have the advantage of providing an in-depth translation of the clinical care process for hospitalised patients, whereas administrative databases only provide an 'accountant view'[3]. Indeed, our methodology allows us to obtain information not only on prescription drugs and diagnoses that can be found in both databases, but also on the patient's medical history and other information such as environmental factors that may contribute to the illness or influence the response to treatment. For example, electronic medical records provide information on smoking, alcohol consumption, weight, presence of side effects or living situations, that can help to better understand disease severity or comorbidities[3].

- The survey

Second, the survey of psychiatrists' attitude toward antipsychotic polypharmacy has followed a rigorous multi-stage development process. First, we had to design and validate each scale that would be used in the survey. For this purpose, we first developed the Resource Generator for Psychiatrists (RG-Psy) so that it could be used to detect the influence of social capital on attitude toward antipsychotic polypharmacy. The RG-Psy items were adapted from the Resource Generator and the Resource Generator-UK, which has already been validated and exhibited good psychometric properties[4,5]. The subsequent validation stages were similar to those for the survey and will be described thereafter.

We also developed the Knowledge and Attitude toward Antipsychotic Polypharmacy Scale (KAAPS) in several steps. The rules for writing the items were scrupulously respected: clarity, avoiding double questions, avoiding double negatives, use of a neutral tone to not induce the most acceptable response[6]. In order to avoid the "yea saying", i.e. people who tend to agree more than disagree, a mix of evidence-based and non-evidence-based items were introduced. We also chose to provide a "do not know" response category, as it has been shown to improve the reliability of responses in knowledge and opinion questionnaires[6], as if this category is not provided, the respondent will answer something by chance. We also chose to use a 7-points bipolar Likert scale (0= Don't know, 1 = totally agree, 2 = agree, 3 = rather agree, 4 = rather disagree, 5= disagree and 6 = strongly disagree), as it is recommended not to use more than 7 categories to measure the strength of an attitude. More than 7 categories are difficult to recall and a scale on 100 is too imprecise. Finally, the length of the instruction and of the items were kept to a medium size (between 16 and 64 words for introduction, and no more than 24 words for each item), because this makes it possible to obtain better quality data[6].

After the items themselves had been drafted, the design of the questionnaire also came under scrutiny. The order of the questions has an impact on understanding and response. When asking questions about attitude, it is preferable to go from the most general to the most specific, but also to group together items on the same subject (e.g. efficacy, adverse effects). The design of a questionnaire also has an impact on the response to questions, which is why we chose to use the Qualtrics® platform, whose design is clear and the space between questions avoids boredom. To avoid too many drop-outs, we established a balance between questions with compulsory answers (mainly for the opinion scale which was the dependant variable) and those that could be ignored[6].

Once the scales had been drafted and designed, their content validity was ensured using cognitive interviews. Cognitive methods aim to detect the

process used by respondents to answer the survey and encompass different techniques such as paraphrasing, vignettes or cognitive interviews[7,8]. Cognitive pre-testing is essential when piloting a questionnaire to avoid measurement error and to ensure that all respondents understand the question in the same way as the researcher intended them to[7]. Of these different methods, cognitive interviewing allows the whole process of answering a question to be explored: comprehension, retrieval, judgement and response. There are two main cognitive interviewing techniques, the think-aloud strategy and the retrospective probing (i.e. retrospectively asking respondents how they arrived at that answer). The think-aloud strategy was used in the development of our questionnaire, as it works better for self-administered questionnaire.[7] In this strategy, respondents are asked to think aloud while answering the questions, in order to detect the path leading to the answer and to understand the reasons for any misunderstanding and how the question was misunderstood. Following the interviews, some misunderstandings were identified and rewording was performed accordingly.

Finally, the administration of the questionnaire must also be determined according to its objective. In order to again avoid the "yea saying" that often occurs in attitudinal surveys, we chose an online self-administered questionnaire, which makes it possible to ask more sensitive questions and to narrow down the most socially acceptable answers. Since the aim was to measure associations between variables, probability sampling was used, which means that each Belgian psychiatrist has the same chance of answering the questionnaire as another, in order to avoid sampling bias in favour of psychiatrists with a certain opinion, for example. To do this, we used the federal list of all psychiatrists authorised to work in Belgium (i.e. "VISA d'exercice"), and searched for their e-mail address or telephone number. If no email was available, a telephone call was made to request their email. This telephone call made it possible to establish a warm contact, i.e. an initial contact before sending the invitation e-mail, which helped to increase the

response rate. Finally, to further enhance the response rate, we sent out a maximum of 3 reminders every 7 to 10 days[6].

- Real-world evidence studies

All our pharmacoepidemiology studies have the advantage of generating real-world evidence. One of the criticisms made by the most sceptical of psychiatric research is the lack of representativeness of the patients included in clinical trials, which can reduce the use of the data generated in this way[9]. Real-world data provides a better representation of the whole population taking the drug under study and is currently used by all health agencies worldwide to monitor effectiveness and safety[9]. In order to better reflect clinical practice in Belgium and to include the entire patient population[10], and thus bridge the gap between research and clinical practice, we used real-world data to measure the impact of withdrawing caffeine on patient outcomes. This has the benefit of not inducing a selection bias, which would probably be the case in a clinical trial, as most heavy caffeine drinkers would probably refuse to take part in such a trial.

In addition, real-world data are also useful for measuring the impact of different healthcare systems and different settings on certain outcomes[10]. This method allows to highlight the key differences between two systems or countries, such as the higher likelihood of deprescribing an antipsychotic during a psychiatric hospitalisation in the Québec hospital, which could stimulate change in the Belgian hospitals.

Finally, the term “real-world evidence” is not only used to refer to epidemiology studies in which interventions are not planned. It can also be used for research taking place in setting other than the traditional one used in most clinical trials, such as large academic centres with clinicians who are familiar with research[10]. This was the purpose of our multi-site PSYCHIC trial, which was a naturalistic study (i.e. carried out into the condition of clinical practice)[11] taking place in non-university hospitals. This has the advantage of including settings where all types of patients could be found, in order to reflect the whole picture of the illness and be as close as possible to routine

clinical care. Indeed, most tertiary care hospitals in Belgium are general hospitals. According to the WHO pyramid framework for mental health care, general hospitals should not be treating patients with severe and complex psychiatric illnesses, such as schizophrenia. Psychiatric wards of general hospitals are generally intended to treat less severely ill patients requiring less intensive care, or patients suffering from drug addictions[12]. As a result, most patients with schizophrenia end up in non-teaching psychiatric hospitals. The design of our study therefore allows a better understanding of the feasibility of therapeutic drug monitoring and genetic tests in everyday psychiatric clinical practice in Belgium.

In addition to being naturalistic, the PSYCHIC trial method must remain robust by having inclusion and exclusion criteria. Certain factors, such as substance use, can be confounding, making it impossible to distinguish between resistance induced by the substance used or by a pharmacogenetic variant. In addition, we measured the efficacy score (CGI) at the same time for all patients (2 and 3 weeks after the start of olanzapine), thus avoiding the bias of some trials comparing CGI measured at different periods of time. As schizophrenia is a highly fluctuating disease, efficacy must be measured at the same moment for all patients, as a CGI at 2 weeks cannot be compared with a CGI at 3 months. In addition, we have chosen to focus on early response, at this is strongly correlated with long-term response. The advantage of this approach is that it avoids excluding patients who have switched antipsychotic in the event of poor response or high burden of side effects, which would be likely to occur if we had measured the CGI at 6 weeks. Furthermore, we chose to use the UKU scale because it is a general scales that cover all possible adverse effects induced by psychotropics[13]. Some studies have focused solely on extrapyramidal symptoms but olanzapine induces very few adverse effects of this type. We also chose to include inpatients only in order to ensure adherence, or at least reduce the risk of poor adherence, as treatment is monitored and poor adherence is more likely to be detected during inpatient than outpatient treatment.

GENERALISABILITY TO BELGIUM

Our first retrospective observational study provides a good representation of the Belgian situation in different settings, since hospitals in the three regions were involved, as well as general and psychiatric hospitals. Our survey was also answered by psychiatrists working in the three regions of Belgium, allowing a good understanding of opinions of Belgian psychiatrists.

MULTIDISCIPLINARY PROJECT

This project has benefited from the input of experts from different disciplines, enabling us to explore the various aspects of the problem of antipsychotic polypharmacy.

The first chapter of the project is a combination of pharmacoepidemiology, psychiatry and clinical pharmacy, while the second brings together sociology of mental health and psychiatry. The pharmacogenetic trial encompasses pharmacokinetics, pharmacogenetics, psychiatry and clinical pharmacology. Taken together, all these disciplines have enabled us to explore the issues raised in this project in greater depth.

UNDERSTANDING THE CONTEXT

Before planning an implementation study, it is important to understand the context[14]. Without this thorough comprehension of the current context and opinions, implementation trials are likely to fail. The strength of this project is that it effectively reflects not only current practices in Belgium regarding the use of antipsychotic polypharmacy, but also current major opinions regarding this prescribing practice. Other information, such as the identification of patients most likely to be prescribed antipsychotic polypharmacy or being deprescribed, or comparison with another country, will be useful for planning future trials. In addition, detecting the influence of social capital on opinions toward antipsychotic polypharmacy will be of great interest for future trials aimed at increasing the use of antipsychotic monotherapy or stimulating antipsychotic deprescribing. Finally, detecting the current barriers to the use of therapeutic drug monitoring and

pharmacogenetic testing has enabled recommendations to be formulated for key stakeholders.

2.3. LIMITS

METHODS

Although the use of medical records for pharmacoepidemiology studies has the advantages described above, it also has its limitations. The databases used are not intended to be used for research purposes, and as a result, inaccuracies or missing information may occur[10]. Interpretation of the data generated must take this limitation into account and be used in conjunction with the results of randomised controlled trials. In addition, randomisation is used to reduce the bias induced by an unbalanced distribution of potential confounders between the groups being compared, which is not possible in pharmacoepidemiology. Thus, research on real-world evidence uses statistical techniques to overcome this limitation, by including potential confounding factors into the multivariable analysis. However, it cannot be ruled out that some confounders remain undetected and are therefore not included in the analysis. However, this limitation does not apply if the objective is to examine patterns of medicines use in clinical routine[10]. The choice of one database over another must therefore be carefully considered in the light of the research objective.

Furthermore, as indicated in chapter II, the relatively low response rate of the survey (12.1%) could limit its generalisability. The response rate of the survey mainly depends on its dissemination methods, which was a self-administered questionnaire sent by e-mail. Physicians are known to have a lower response rate to online surveys than the rest of the population[15,16], due to lack of time and the cumbersome nature of the survey[17], with psychiatrists having the lowest response rate of all specialists[17]. Nevertheless, recent research has established that a low response rate does not necessarily generate biased results, and that conversely, a higher response rate does not protect against biased results[18,19]. It has been previously demonstrated that excluding late

and difficult-to-reach respondents does not produce a significant difference in the survey results[19], and that it is more appropriate to compare the characteristics of non-respondents with those of respondents. Analyses of our survey indicate that non-respondents do not differ from respondents in their demographics. The second limitation of our survey is the absence of opportunity to clarify questions, since it was an online self-administered questionnaire, and we had missing data that we had to impute. However, choice of methods must be weighed against the advantage of using a self-administered questionnaire, that were detailed above.

Finally, in our PSYCHIC trial, where patients were included for up to 3 weeks, we were unable to detect any long-term adverse effects, such as metabolic syndrome. However, the short-term side effects common with olanzapine could be detected, such as daytime sedation or anticholinergic side effects. The choice to explore efficacy and short-term side effects was made deliberately to avoid an indication bias that could have been induced by poor responders being switched to another antipsychotic by the time of blood sampling and administration of the CGI and UKU scales, thereby excluding those patients.

GENERALISABILITY TO OTHER COUNTRIES

Although our first retrospective study provides a good picture of Belgian hospitals, our second study on deprescribing antipsychotic compares the Belgian situation with that of a single hospital in Québec. We cannot therefore generalise the comparison to the whole situation in Quebec or even Canada. However, the example of a very different prescribing pattern in another country or culture could stimulate change in Belgium.

STUDIED POPULATION

The choice of age group included may raise questions. Indeed, we focused on adult patients with schizophrenia. One of the aims of our project was to assess the appropriateness of psychotropic prescribing patterns in schizophrenia. Children, adults and the elderly do not exhibit the exact same pharmacokinetic and pharmacodynamic response to drugs (i.e. side effects,

efficacy), and consequently the benefit/risk balance of drugs is different in these different age categories. For example, in older adults with schizophrenia, it is recommended that an antipsychotic with weak anticholinergic properties that has been studied in older adults should be chosen first (e.g. risperidone), whereas anticholinergic properties are not a barrier to their use in adult patients with schizophrenia, as the benefit/risk ratio is still positive in this population. To study the relevance of prescribing psychotropic drugs in both the adult and elderly populations, two studies or a subgroup analysis would have been required in each case. This would have required the inclusion of a sufficient number of elderly patients with schizophrenia, which would have been difficult to reach due to the shorter life expectancy of these patients. In addition, many older patients with schizophrenia also suffered from comorbid dementia. This would have made the assessment of the appropriateness of the prescription of antipsychotics even more difficult, as another subgroup would have been analysed (i.e. older patients with a dual diagnosis of schizophrenia and dementia), and this would have been outside the scope of the project. Moreover, given that schizophrenia affects a majority of adult patients (i.e. about 70% of patients with schizophrenia), we considered it more appropriate to focus on the schizophrenia population most exposed to potentially inappropriate prescribing, i.e., the adult population with schizophrenia. Finally, as inappropriate prescribing in schizophrenia exposes patients to the long-term side effects of antipsychotic (e.g. diabetes, tardive dyskinesia), we felt that the greatest effort to deprescribe should be made early in the course of the disease, to prevent them.

3. CLINICAL PERSPECTIVE

Findings of this thesis provide perceptive for improving pharmacotherapy in psychiatric clinical practice.

3.1. RECOMMANDATIONS FOR PSYCHIATRISTS

USE OF THERAPEUTIC DRUG MONITORING TO ENSURE TREATMENT ADHERENCE AND PLASMA CONCENTRATIONS WITHIN THERAPEUTIC RANGES

As discussed previously, adherence to treatment is a challenge in schizophrenia, with more than a third of patients each year being non adherent[20]. Unfortunately, lack of adherence is often underestimated by psychiatrists, as up to 94% of poorly adherent patients are considered by their physician to be taking their treatment well[21]. Mislabelling patients as being adherent can lead to dose increases or unnecessary polypharmacy[21]. Prescribing long-acting injectable (LAIs) antipsychotics is one way of ensuring compliance, but they are prescribed less in Belgium than in Québec, probably because they are reserved for patients in whom poor adherence has been detected in Belgium. Therapeutic drug monitoring (TDM) has been shown to be better at detecting adherence to treatment than patient self-assessment or clinician assessment, as it is an objective measure[22]. Plasma concentration measurement of antipsychotics is currently rarely performed in Belgium, so we recommend that therapeutic drug monitoring be performed as part of routine care, even for patients assumed to be adherent, and that LAIs and/or a psychoeducation programme be considered when poor adherence is identified[23]. In addition, as shown in our PSYCHIC study in Chapter III, TDM can also detect plasma concentrations outside the therapeutic range. Thus, to guarantee the best possible outcome, TDM should also be part of the routine to ensure that the patient is within the therapeutic range.

WAITING

In the PSYCHIC study, we found that many patients were prescribed a second antipsychotic in addition to another within a few days of admission to hospital. This is consistent with previous trials where the majority of patients were prescribed APP within 90 days of starting an antipsychotic[24]. We also found that 70% of patients in whom clozapine was introduced were directly started on a clozapine-antipsychotic polypharmacy. While a trial of approximately 6 weeks of an antipsychotic is currently recommended by clinical prescribing guidelines, this is currently being questioned as it has been shown that an early response or lack of response can be assessed after up to 2 weeks of treatment [25-27]. However, it is important to wait at least two weeks and to ensure that other non-response factors have been eliminated before switching to another antipsychotic. In addition, in cases of treatment resistance (i.e. failure to respond to two trials of antipsychotics at an adequate dose and duration), clozapine should be prescribed, as polypharmacy is too often used instead of clozapine, delaying its introduction[24].

REEVALUATION OF LOW DOSE SEDATING ANTIPSYCHOTICS

In Belgium, schizophrenic patients are overwhelmingly prescribed low-dose sedative antipsychotics for sleep disorders, with 22.1% and 29.3% respectively on admission and at discharge from psychiatric hospitalisation. The comparison of these trends with those observed in the Canadian hospital, where only 1.6% and 4.8% of patients were taking a low-dose antipsychotic at admission and discharge respectively, raised questions. In addition, during the PSYCHIC study, we identified several patients who had been prescribed a low-dose antipsychotic and who refused to take it at bedtime because they did not have sleep problems. Due to recent concerns about the safety of such prescribing (i.e. more cardiovascular adverse events with low-dose quetiapine, drug-drug interaction with low-dose levomepromazine, neuroleptic malignant syndrome reported with low-dose clotiapine), we recommend that prescribing a low-dose antipsychotic in addition to an antipsychotic should be regularly re-evaluated.

REEVALUATION OF THE PRESCRIBING OF ANTICHOLINERGIC DRUGS

About 10% of Belgian patients admitted in the studied Belgian hospitals have been prescribed anticholinergic drugs, used to treat extrapyramidal symptoms. This prevalence increases significantly on discharge from hospital. Conversely, in Canada, about 20% of patients were admitted on anticholinergics, but only 9.5% were taking them at discharge, indicating that they had been deprescribed during their hospital stay. These drugs induce numerous side effects (e.g. blurred vision, constipation, urinary retention), which may be aggravated if they are combined with drugs that already have anticholinergic effects. We recommend that the prescription of anticholinergics should be regularly reassessed, particularly when a patient is switched from an FGA to an SGA, which already have a high anticholinergic effect.

CONSIDERING CLOZAPINE MONOTHERAPY

Approximately 10% of schizophrenic patients hospitalised in the Belgian hospitals studied were prescribed clozapine, although up to a third of them were eligible. In addition, being eligible for clozapine (i.e. having had two previous trials of antipsychotics) was associated with a greater likelihood of being prescribed APP. The response rate to clozapine can be as high as 80% when it is introduced early in the course of the disease, whereas it is only 30% when it is introduced with a delay of 2.8 years or more[23].

Reminders to introduce clozapine after 2 trials of antipsychotics, instead of APP, should be made in clinical practice. Furthermore, as we have seen previously, approximately 70% of patients in whom clozapine was introduced were started directly on clozapine-antipsychotic polypharmacy. We therefore recommend that clozapine should first be tried as monotherapy for a sufficient period. Response to clozapine takes longer than with other antipsychotics, with 30% response after 6 weeks, a further 20% after 3 months and 10-20% after 6 months[23]. It is therefore recommended that clozapine be tried for at least 6 months as monotherapy.

Box 1- Recommendations for psychiatrists based on identified current Belgian practice

- Ensure treatment-adherence with therapeutic drug monitoring before increasing the dose, switching or adding a second antipsychotic
- Wait at least 2 to 3 weeks, and exclude other factors of non-response, before increasing the dose, switching or adding a second antipsychotic
- Regularly reassess the legitimacy of prescribing low-dose antipsychotics for sleep disorders
- Regularly reassess the prescription of anticholinergic drugs, especially when switching to a second-generation antipsychotic
- Do not delay the introduction of clozapine monotherapy
- Do not use APP instead of clozapine for treatment-resistant schizophrenia
- Try clozapine monotherapy for a sufficient period of time (6 months) to assess clinical response

3.2. PROMOTING THE APPROPRIATE USE OF ANTIPSYCHOTICS IN SCHIZOPHRENIA

Although the treatment of schizophrenia has long been focused on symptom reduction, it is time to move from this perspective to one of recovery, and therefore to avoid inappropriate polypharmacy that increases the drug burden and contributes to worsening functional outcomes and subjective well-being[28].

However, many difficulties arise when trying to introduce evidence and guidelines into clinical practice. There are different strategies for changing medical practice, with different levels of effectiveness. Some of these strategies will be examined to find ways to reduce the prescribing of antipsychotic polypharmacy.

LOCAL OPINION LEADERS

Implementation of evidence is influenced by context. There is a wide range of definitions of context, but it can be summarised as the environment, setting, healthcare organisation, political will and the culture, knowledge, and attitude of professionals[14].

As our survey showed, opinion toward antipsychotic polypharmacy is influenced by social capital and also confirms the theory of structural holes, as psychiatrists with the greatest social capital were less likely to have a positive attitude toward antipsychotic monotherapy (i.e. the innovation). This means that it has not yet penetrate the dense network of Belgian psychiatrists. To avoid 'echo' and bridge gaps, new physicians should be encourage to establish more frequent contact with scientists or physicians outside their network[1]. Local opinion leaders could be a means of spreading evidence-based practices within the network in order to gradually change the "major" attitude. Opinion leaders do not necessarily have the highest position or status in the system, but they are the most likely to influence the attitude and behaviour of individuals through informal leadership. Confirming the theory of structural holes, opinion leaders tend to have more external communication and are therefore often at the centre of interpersonal communication between networks. They are thus exposed to a greater flow of information and innovation. Opinion leaders can give lectures but also informal education sessions[29]. The effectiveness of opinion leaders in promoting evidence-based practices is mixed and influenced by context and combination with other interventions. For example, opinion leader interventions may be more effective in hospital settings than in primary care, where networks are sparser and diffusion more complex[29].

The main limitation of this strategy is the formal identification of opinion leaders, who are not necessarily official leader by their status[29].

EDUCATIONAL SESSIONS

Cognitive theories suggest that the low use of evidence is influenced by insufficient knowledge of the poor outcomes of current practice[2]. However,

the provision of educational materials alone is only modestly effective if used alone. Educational sessions have been shown to be more effective in improving the use of evidence, particularly when groups are small and sessions are interactive[2].

Based on the results of our survey, we were able to better detect situations where the use of antipsychotic polypharmacy was still considered justified by the majority of psychiatrists and situations where it is unclear whether it is appropriate or not. This will enable these situations to be specifically addressed during training sessions.

Box 2. Misperceptions to be addressed during educational sessions

- Use of APP for patients with a dual diagnosis of schizophrenia and substance use disorder leads to further improvement
- Use of APP for patients with a dual diagnosis of schizophrenia and intellectual disability leads to further improvement
- The use of APP is appropriate after insufficient response to monotherapy
- APP is used to combine different pharmacological profile
- APP is appropriate for the management of sleep disorders

These educational sessions must be combined with other interventions, as multifaceted interventions are more effective than a single strategy.[2]

CLINICAL DECISION SUPPORT SYSTEMS (CDSS)

"Today, no one clinician can retain all the information necessary for sound, evidence-based practice. No unaided human being can read, recall, and act effectively on the volume of clinically relevant scientific literature" says the US Institute of Medicine[30]. Therefore, another option to let clinicians know of the latest evidence or remind them of best practices is to use information technology, such as clinical decision support systems (CDSS)[2].

As CDSS is a software aimed to aid in clinical decision making in which characteristics of individual patients (e.g. age, glomerular filtration rate) are

matched to a computerized knowledge base in order to generate patient-specific assessments or recommendations that are then presented to clinicians for consideration[31]. CDSS can assist physicians for prevention and monitoring, prescribing of drugs and also diagnosis and management[30]. Numerous trials have shown that CDSS improve physician performance and produce a clinically important effect (i.e. better patient outcomes), especially for drug prescribing and preventive care[31]. In addition, the implementation of CDSS has been shown to significantly reduce medication errors[32] and preventable adverse drug events[33]. The rate of medication errors in psychiatric hospitals varies from 10.6 to 17.5 per 1000 patient-days and most often concerns atypical antipsychotics[34]. The prevalence of adverse drug events in psychiatric hospitals ranges from 10 to 42 per 1000 patient-days, of which 13 to 17% are avoidable[35]. Before implementing a CDSS in psychiatry, criteria are needed to help detect inappropriate prescribing. The evidence incorporated into the CDSS can be extracted from clinical guidelines. However, to improve uptake, peer endorsement is of great importance, as discussed above. A recent study used a Delphi method to established a list of "safety indicators" related to the prescribing of medicines for mental health disorders[36]. The Delphi method is "a structured consensus method that uses a series of questionnaires or rounds to obtain the most reliable consensus of opinion of a group of experts"[36]. A list of 42 safety indicators has been published and could be used as a basis for integration into CDSS. For example, the prescription of APP for more than 2 months is considered inappropriate in this list, in order to avoid including switch situations between 2 antipsychotics[36]. This could trigger an alert, aimed at reminding the clinician of the need to reassess the prescription.

Some CDSS could also provide a real-time monitoring of habits, such as APP, which could help monitor this practice and the effect of different interventions[37].

However, CDSS alerts can lead to alert fatigue, which could lead to high override rates[38]. Alert fatigue is likely due to cognitive overload (i.e. receiving a large amount of information with a lack of time or cognitive resources to

distinguish relevant from irrelevant information[38]) and desensitization (the alert is more effective at first notice, because individuals acclimatised to it overtime)[38]. Alert fatigue lead to bypass of alerts, which is more likely to occur with work complexity and repeated alerts, although it is not related to workload[38]. CDSS can therefore sometimes suffer from a negative attitude which can create of barrier to the acceptance of CDSS alerts. As it has been shown that 5 adverse drug events occur every 100 alerts bypassed[39], this issue needs to be seriously considered if CDSS is to be used to improve guidelines adherence in schizophrenia. However, this barrier is again more about attitude than knowledge, and CDSS is more likely to work better on clinicians who are already convinced but lack the time to keep up to date with the latest evidence.

INTERPROFESSIONAL COLLABORATION WITH CLINICAL PHARMACISTS

Management of polypharmacy requires the combined knowledge of physicians, nurses, pharmacists and other healthcare professionals[40]. Clinical pharmacists have been integrated into multidisciplinary mental health care teams for over 50 years in the US to ensure safe and effective prescribing practices in order to improve patient outcomes[41]. The roles of clinical pharmacists are various and encompass treatment recommendations, delivering education to psychiatry staff, identifying drug interactions and patient education[41]. Integration of clinical pharmacists into mental health teams has been shown to improve outcomes, prescribing practices, patient satisfaction and resource use (e.g. primary care visit, costs), suggesting the model to be cost-effective[41].

For example, clinical pharmacists have been shown to effectively detect drug-related problem (DRP) in psychiatric inpatients. DRP is defined as problems in the pharmacotherapy of the individual patient that actually or potentially interfere with desired health outcomes. In psychiatric hospitals, about 2.5 DRP are found during each medication review by a clinical pharmacist, most of which relate to drug dosing, inappropriate drugs or interactions, with olanzapine and quetiapine being the drugs most frequently represented in

DRPs.[42] Based on this evidence, many hospitals around the world have implemented medication review by clinical pharmacists[42]. However, although the American College of Psychiatry has long endorse the expertise of clinical pharmacists in drug interactions identification, treatment recommendation and education[41], in Belgium, there is still a lack of support for clinical pharmacy activities. Federal funding is limited to 0.5 full time clinical pharmacist per 200 beds, whereas the Europe average is 1 full time clinical pharmacist per 100 beds[43]. In addition, the current shortage of hospital pharmacists in Belgium does not encourage the development of clinical activities, particularly in smaller hospitals such as psychiatric hospitals. In order to optimise the workforce utilisation, a pharmacist-physician collaboration based on the "Eichberger model" could be proposed. In such model, clinical pharmacists do not visit wards on a daily basis or work there full time, but physicians send requests to the pharmacists on a day-to-day basis, and problems are then discussed during ward rounds every 2 weeks, while some topics can be discussed during phone calls[43]. This model works well in psychiatric hospitals, where about 80% of psychiatrists contact the pharmacist for request about appropriate drug selection, drug interaction, possible adverse drug event and drug switching, with a 100% acceptance rate[43].

Besides, clinical pharmacists could be used in combination with CDSS to help manage CDSS alerts, as they are often override[38], leading to adverse drug events[39]. However, clinical pharmacists are also prone to alert fatigue[38]. Therefore, the use of information technologies could help prioritizing interventions of clinical pharmacists, in a perspective of optimizing the use of healthcare workforce.

Nevertheless, more multidisciplinary collaboration needs to be promoted to meet patient expectations and improve patient outcomes, as innovations evolve more rapidly than our ability to implement them[30].

REGULAR EVALUATION OF PRACTICE AND PERFORMANCE FEEBACK

Audit and feedback lead to small but potentially important improvements in evidence uptake and professional practice, but this depends on the type of feedback and the clinical behaviour targeted[2,44]. Feedbacks lead to better practice improvement when the performance baseline is low, the feedback is delivered by a supervisor or a colleague, given more than once, both written and orally and includes explicit objectives and action plan[44]. Thus, it should be combined with educational session, outreach visit or reminders (e.g. CDSS)[2]. In addition, peer comparison through feedbacks has been shown to improve antipsychotic prescribing practices[45], and could be implement in Belgium.

3.3. RECOMMANDATIONS FOR KEY STAKEHOLDERS FOR IMPROVING PSYCHIATRIC PHARMACOTHERAPY

Even when clinicians are aware of the latest evidence and willing to change, they may not do so if their environment does not encourage them do to so[2]. Indeed, although Belgium has the second highest number of psychiatric beds per capita in Europe (after Malta) and among OECD countries (after Japan), with 141 beds per 100,000 inhabitants[46], the number of psychiatrists is similar to the OECD average (0.17 psychiatrists per 1,000 inhabitants). This means that there are far fewer psychiatrists per patient hospitalised in a psychiatric ward in Belgium than in other OECD countries. The number of psychiatrists should be increased in Belgium, to allow more time to reassess the treatment of each patient during psychiatric hospitalisation. In addition, payment policies strongly influence the way care is delivered. Current authorities should remove the barriers to quality improvement, for example by offering financial incentives or adapting paying method[30] for hospitals that have a quality improvement plan strategy for psychotropic prescribing practices. Financial interventions have proved to improve prescribing practices and reduce drug costs[2].

In addition, as reducing access to caffeine can improve patient functioning and shorten hospital stays, and is an inexpensive and easy to implement

policy, caffeine may be removed from inpatient wards for patients with schizophrenia. However, there is some evidence suggesting that caffeine consumption may reduce the risk of depression[47]. This measure should therefore be taken with caution in patients diagnosed with schizoaffective disorder.

Box 3 - Recommendations to policymakers regarding incentives to improve the quality of psychotropic prescribing

- Provide financial incentives to hospitals that have a strategic plan to improve psychotropic prescribing practices
- Regularly monitor the use of antipsychotic polypharmacy in severe mental illnesses and offer a financial incentive to those who reach a predefined threshold

Unfortunately, regulation is often characterised by a patchwork that is slow to adapt to change[30]. In Belgium, current policies focus on the move towards outpatient mental health care, with little emphasis on the appropriate prescription of psychotropics to adult patients with mental disorders.

In addition, the provision of education material alone has shown limited effectiveness, but this is the strategy currently adopted by the Belgian authorities, with an interactive website available for the deprescribing of benzodiazepines, antidepressants and other hypnosedatives[48]. Although this website provides a wide range of information, it has been little advertised, and the results are unlikely to be significant unless combined with all the strategies described above (e.g. CDSS, clinical pharmacy services, educational sessions, opinion leaders). Furthermore, outreach visits by non-commercial pharmacotherapy educators are no more funded, leaving the door open to industry delegates alone. There is a risk of promoting antipsychotic polypharmacy, as a commercial brochure on cariprazine recently did.

Box 4 - Recommendations to policymakers and hospital stakeholders regarding clinical pharmacy services

- Funding at least 1 clinical pharmacist per 100 beds, in line with the European average, to assist psychiatrists in psychotropic and non-psychotropic drugs prescribing
- Modify the organisation of hospital pharmacies to redirect the staff toward clinical activities

Box 5 - Recommendations to policymakers and hospital stakeholders regarding CDSS

- The setting up of CDSS in all psychiatric hospitals should be encouraged, either by financial incentives or by legislation in order to improve the quality of psychotropic prescribing

Box 6 - Recommendations to policymakers regarding peer feedback

- Anonymous peer comparison (i.e. no hospital identification) to monitor the use of antipsychotic polypharmacy compared to other hospitals and stimulate change, based on the antibiotic stewardship model

In addition, there are currently many courses in basic psychopharmacology but insufficient training in clinical psychopharmacology and psychopharmacotherapy in pharmacy schools. Funding for specialist training in psychopharmacotherapy should be promoted for hospital pharmacists, but also for community pharmacists. At least one specialist in clinical psychopharmacology should be funded in each psychiatric hospital.

Box 7 - Recommendations to policymakers regarding the training of pharmacists

- Fund the training of more hospital and clinical pharmacists to make up for the current shortage, which is preventing the development of clinical activities, particularly in psychiatric hospitals
- Develop specialist training in clinical psychopharmacology for pharmacists, in order to reduce the knowledge deficit that is preventing the development of consultancy services by clinical pharmacists

Finally, a major obstacle to the use of therapeutic drug monitoring to detect low plasma concentration or poor adherence is the lack of its reimbursement in Belgium. Measuring the plasma concentration of an antipsychotic is only reimbursed in the event of intoxication, which limits its use in routine clinical practice. Funding for TDM in clinical routine could improve the detection of poor response due to low plasma concentration of antipsychotics.

Box 8- Recommendations to policymakers regarding the reimbursement of therapeutic drug monitoring and pharmacogenetic tests

- Reimburse therapeutic drug monitoring for antipsychotics on a daily basis

4. RESEARCH PERSPECTIVE

This thesis project has filled certain gaps in the research, which is also generating new research questions.

In addition, numerous studies have been published or are still underway with the aim of testing different combinations of antipsychotics in search of superior efficacy. In the absence of a new drug with a different pharmacological profile, and given current knowledge of the pharmacology

of antipsychotics, funding research into combinations of several antipsychotics could be seen as a waste of money and time. To take better use of resources, research should now focus on strategies for deprescribing antipsychotics to achieve antipsychotic monotherapy, with the help of therapeutic drug monitoring and pharmacogenetic, in order to find the right dosage for the right patient and improving patient outcomes.

4.1. OPINIONS AND INVOLVEMENT OF OTHER HEALTHCARE PROFESSIONALS AND PATIENTS INTO THE DEPRESCRIBING OF ANTIPSYCHOTICS

The majority of studies have focused on psychiatrists'opinion toward antipsychotic polypharmacy, who are the main professionals involved in changing the prescription of antipsychotics for schizophrenia. However, little is known about the involvement of other healthcare professionals. Nurses requests for an "as needed" antipsychotic or the addition of another drug has been cited as a factor contributing to antipsychotic polypharmacy[49]. As nurses are the healthcare professionals closest to patients during hospitalisation, their attitude regarding pharmacotherapy is greatly valued and listened. Moreover, educational sessions for nurses have had some success for example in Switzerland. In addition, as the psychiatry is a highly multidisciplinary field, where many professionals are involved in the care of patients with schizophrenia, the attitude of psychologists, occupational therapists and social workers would be of great added values. As far as outpatient care is concerned, the involvement of general practitioners in deprescribing antipsychotics for schizophrenia is unknown. As these physicians are often heavily involved in deprescribing other medicines, it would be useful to understand their involvement in schizophrenia and whether it is different from that of other drugs or other diagnosis. Community pharmacists are also involved in delivering antipsychotics to patients with schizophrenia, but they have little training in this area. It would be interesting to know their opinions and knowledge of this pharmacotherapy. Previous studies have also highlighted the stigma community pharmacists have toward this population, and it would be interesting to integrate this into the

dimension of deprescribing, as this may constitute a barrier to deprescribing[50]. Finally, although patient barriers are often mentioned as important obstacles to deprescribing benzodiazepines or antidepressants, patient wishes are rarely mentioned by psychiatrists as a reason for leaving a patient on antipsychotic polypharmacy. One of the main reasons for this may be that, unlike other psychotropic drugs such as benzodiazepines, for which patients develop dependence, the opposite pattern seems to be associated with antipsychotics in schizophrenia. Indeed, adherence to antipsychotics is challenging in schizophrenia, with up to 50% of schizophrenic patients being non-adherence[21], and is reduced by polypharmacy[23]. For this reason, some guidelines advise against antipsychotic polypharmacy in poorly adherent patients[23]. This highlights that many patients do not want to take multiple medications in schizophrenia, which may be supported by the result of our first study where involuntarily admitted patients were less likely to receive antipsychotic polypharmacy, perhaps because their reluctance towards care in general and therefore medication protects them from this prescribing pattern. Thus, the main effort to avoid prescribing antipsychotic polypharmacy should be made as early as possible, for example during acute hospitalisation for a first psychotic episode, when patients are often admitted involuntarily and therefore cannot choose their treatment. This explains why almost all trials have focused on clinicians' rather than patients' views of antipsychotic polypharmacy. However, it cannot be ruled out that some patients are currently being prescribed antipsychotic polypharmacy over a long period as outpatients. These stable patients who have not been hospitalised for a long time could not benefit from hospital-based interventions aimed at reducing the use of antipsychotic polypharmacy. It would therefore be particularly interesting to know their opinion on this specific prescribing pattern. This would make it possible to overcome certain prejudices, as this was the case with the prescription of long-acting antipsychotics, where many clinicians claimed that the main barriers to this prescription came from the patients, whereas in surveys of patients, the majority showed a clear preference toward long-acting injectable

antipsychotics[51]. It would therefore be very interesting to hear the voice of patients in future studies.

4.2. FURTHER EVALUATION OF PHARMACOTHERAPY-RELATED SAFETY ISSUES

Besides antipsychotic polypharmacy, other suboptimal prescribing patterns have been identified in the Belgian hospitals. However, there are currently no study using a list of potentially inappropriate prescriptions in psychiatry to detect their prevalence in Belgian hospitals. The list of 42 safety indicators for medicines prescribed in mental illnesses could be used for such investigation[36]. In addition, identification of the medication errors that lead to preventable adverse drug events in psychiatric units or hospitals could be valuable to raise awareness and promote the implementation of strategies to improve the pharmacotherapy of psychotropics.

4.3. IMPROVING UPTAKE OF LATEST EVIDENCE IN PSYCHIATRY

In order to improve the uptake of the latest evidence into clinical practice, and therefore improve the quality of psychotropic prescribing, different simple implementation trials could be tested, such as educational sessions made by different trainers, or integrating safety indicators into a CDSS.

In addition, more complex implementation trials and/or research actions could be undertaken, particularly targeting patients least likely to be deprescribed, as others could benefit from simpler interventions. An example of a complex intervention could be the use of a CDSS incorporating alerts for deprescribing, therapeutic monitoring of drugs and/or pharmacogenetic testing, combined with supervision by a clinical pharmacist, clinical biology specialists and psychiatrists. Such study could assess the feasibility, acceptability and clinical effectiveness of such interventions. The difficulty of recruiting centres could be examined in depth, and opinion leaders could help

convince more centres to participate. In addition, more funding would be needed to increase centre participation. Contrary to popular belief, patient recruitment is not the main obstacle, as around 45% of patients agreed to take part in our latest PSYCHIC study, which is in line with expectations. This prejudice should be overcome to convince more centres to participate, as many of them think that such a study is not feasible. Finally, a study nurse would be required at each centre to ensure screening and supervision of protocol compliance, such as the appropriate timing and handling of blood samples for therapeutic drug monitoring.

4.4. ECONOMIC EVALUATION

The cost of a clinical pharmacy services is often a barrier to its implementation. However, recent studies found that adherence to schizophrenia prescribing guidelines decrease cost and increase quality-adjust life-years[52]. Few studies have tried to evaluate the cost of such services. A study in the USA found a 40.000$ cost avoidance per psychiatric pharmacy resident, but the healthcare system of this country is greatly different from the one of Belgium. The calculation focused on adverse drug events (ADE), by multiplying the cost of an ADE by the probability that the ADE would have happened if the intervention has not occurred. They don't include the possible cost reduction induced by the decrease in the number of drugs dispensed. Nevertheless, antipsychotic were the drugs implicated in the greatest cost avoidance. Based on this trial, a pharmacoeconomic evaluation of psychiatric clinical pharmacist could be performed in Belgium.

Further exploring barriers to deprescribing	
Qualitative study and/or survey	Detection of the opinions and self-efficacy of general practitioners regarding the deprescribing of antipsychotics in schizophrenia
	Identification of nurses and other healthcare professionals (e.g. psychologists, social workers) knowledge and attitude toward antipsychotic polypharmacy and deprescribing in schizophrenia
	Detection of patient perceptive regarding the deprescribing of antipsychotics in situation of antipsychotic polypharmacy
	Evaluation of the influence of nurses and other healthcare professionals on deprescribing psychotropics
Further evaluation of pharmacotherapy-related safety issues	
Pharmacoepidemiology	Identification of prescribing errors in Belgium using safety indicators in outpatient and inpatient settings, and in several psychiatric illnesses
	Identification of adverse drug events and prevalence of preventable ones in psychiatric care in Belgium
Improving uptake of latest evidence in psychiatry	
Implementation	Evaluation of the impact of educational sessions on opinion changes regarding antipsychotic polypharmacy. Comparison of session made by different trainers (e.g. colleague, supervisor, clinical pharmacist) to detect the most effective strategy
	Evaluation of the effect of integrating safety indicators into a CDSS on the quality of prescribing in Belgian psychiatric care
Implementation trials-research action	Complex medication review combining clinical pharmacists, therapeutic drug monitoring, pharmacogenetic testing and clinical decision support system to detect improvement in specific targeted prescribing issues (e.g. reduction in prescribing of antipsychotic polypharmacy, increase in prescribing of clozapine to treatment-resistant patients, optimizing the prescription of antipsychotics): acceptability and clinical impact
Pharmacoeconomics	
Pharmacoeconomic evaluation	Pharmacoeconomic evaluation of the impact of clinical pharmacy services specialised in psychopharmacology that help guide prescribing of psychotropic drugs: evaluation of different options such as on-ward full time, on-ward weekly meeting, hotline service, the Eichberger model

5. CONCLUSION

The prescription of antipsychotics, the cornerstone of schizophrenia treatment, is currently sub-optimal in Belgium. This situation prevents patients from receiving the best available care, reducing their functioning and therefore their path to recovery. Patients the most at risk of mis-prescription such as antipsychotic polypharmacy, identified in this project, could be specifically targeted by interventions. Improvement in prescribing practices, such as deprescribing of inappropriate polypharmacy, could be reinforced by drawing on strategies from other countries or by using the social capital of psychiatrists. In addition, detection of the plasma concentration of antipsychotics and pharmacogenetic tests could be encouraged when there is a lack of appropriate response or particularly significant side effects. The use of complex intervention strategies should be encouraged in order to achieve better pharmacotherapy for patients with schizophrenia.

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APPENDIX

Appendix to the PSYCHIC trial protocol useful for understanding the project

Appendix 1- Clinical Global Impression (CGI) scale

What is the clinical global impression scale (CGI) ?

The CGI is a scale that has been developed to assess the patient's global functioning prior to and after initiating a medication. It is an overall measure that takes into account all available information including patient's history, psychosocial circumstances, symptoms, behavior and the impact of the symptoms on the patient's ability. The aim of the CGI is to capture the clinical impression instead of a symptoms 'checklist.

The CGI takes 1 minute to be completed, and is very understandable and intuitive. In addition, it shows a good correlation with other scales used in clinical research that are more time consuming and arduous (i.e. PANSS, BPRS).

The CGI has to be administered by a clinician who is familiar with the disease and with the progression under treatment.

The source of information is the clinical interview with the patient, but can also be combined with information available in medical chart's, from family members, social workers, unit nurses or other patient's relatives.(1)

Please, use the Study form (Appendix 14), available in the investigator's chart, to note the CGI scores of your patient.

1) The CGI-S

The CGI-S aims at evaluating the severity of the psychopathology of your patient from 1 to 7, at the time of admission in the unit.

"Considering your total clinical experience with this particular population, how mentally ill is the patient at this time ?"

CGI-S (Severity)	
1	**Normal, not at all ill** Symptoms of disorder not present past seven days
2	**Borderline mentally ill** Subtle or suspected pathology
3	**Mildly ill** Clearly established symptoms with minimal, if any, distress or difficulty in social and occupational function
4	**Moderately ill** Overt symptoms causing noticeable, but modest, functional impairment or distress; symptom level may warrant medication
5	**Markedly ill** Intrusive symptoms that distinctly impair social/occupational function or cause intrusive levels of distress
6	**Severely ill** Disruptive pathology, behavior and function are frequently influenced by symptoms, may require assistance from others
7	**Among the most extremely ill patients** Pathology drastically interferes in many life functions; may be hospitalized

2) The CGI-I

The CGI-I aims at evaluating the change from the initiation of the treatment on a scale from 1 to 7. The CGI-I can follow clinical progress over time.

The CGI is rated without regard to the clinician's belief that the progress is due to the antipsychotic and without consideration of the etiology of the symptoms.

"Compared to the patient's condition at admission to the hospital, this patient's condition is:"

CGI-I (Improvement)	
1	**Very much improved** Nearly all better; good level of functioning; minimal symptoms; represents a very substantial change
2	**Much improved** Notably better with significant reduction of symptoms; increase in the level of functioning but some symptoms
3	**Minimally improved** Lightly better with little or no clinically meaningful reduction of symptoms. Represents very little change in
4	**No change** Symptoms remain essentially unchanged
5	**Minimally worse** Slightly worse but may not be clinically meaningful; may represent very little change in basic clinical status or functional capacity
6	**Much worse** Clinically significant increase in symptoms and diminished functioning
7	**Very much worse** Severe exacerbation of symptoms and loss of functioning

3) Example of the use of the scale

"A 34-year-old, male patient with a diagnosis of paranoid schizophrenia has attended a partial hospitalization program off and on for 12 years. According to his caseworker, he had been stable on his medication regimen for the past year, but recently stopped taking his medication and would not cite a reason. He attended the partial program only one of the expected four days this past week and this was after the caseworker went to his home and drove him to the treatment facility. The caseworker reports he has become increasingly threatening and difficult to manage and has been seen responding to auditory hallucinations, including taking cover behind furniture in attempts to hide from "enemies." In the past week, he obeyed a command hallucination to "go after" a fellow patient, but was physically circumvented from harming the patient by three staff members, who physically restrained him. The caseworker reported that although the patient was passively cooperative about coming to today's visit, he did not speak with her at all during the trip. In the office, he is guarded and suspicious. He mumbles under his breath, but refuses to elaborate as to what he has said or to whom it was directed. Twice he makes a fist and raises his arm threateningly in the direction of the psychiatrist, but then puts his hand back in his lap. He appears disheveled and is ungroomed; he has not changed his clothing over the past week, which his caseworker reports is a new behavior for him."

Suggested CGI-S score=6 (severely ill)

Rationale: The patient's functioning is clearly affected by his symptoms to the extent that he is not attending his day treatment program or taking his medication. Previously well groomed, he has now stopped even basic elements of self-care and hygiene. His behavior required restraint and may have posed a physical risk to others. This is a patient one might actively consider hospitalizing. Based upon his disruptive pathology and behavior influenced by symptoms (hallucinations), a CGI-S score of 6 (severely ill) is warranted. This patient did attend his day treatment program one day and did willingly accompany the caseworker to his visit with the psychiatrist, suggesting a somewhat lessened level of severity than a 7 would imply. (1)

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Appendix 2- UKU-patient-English version

Patient anonymisation code : …….. Date : …….

We wish to know how you experience the medication you are prescribed. For each symptom/discomfort mentioned below, we ask you to check the alternative that best corresponds to your condition during the past 2 weeks. Do not check any alternative, if you cannot answer for any reason.

1. Psychic functions

1.1 Do you have difficulties in collecting your thoughts, or understanding the context when you are reading, talking to somebody, watching TV or listening to the radio?

□ Not at all
□ A little more than usual
□ More than usual
□ Much more than usual

1.2 Do you feel tired, or do you quickly become exhausted, or do you need to rest often in order to manage to continue your activities?

□ Not at all
□ A little more than usual
□ More than usual
□ Much more than usual

1.3 Do you feel sleepier than usual, or is it difficult staying awake during the daytime?

□ Not at all
□ A little more than usual
□ More than usual
□ Much more than usual

1.4 Have you noticed that you are more forgetful than usual, or that you do not remember simple things, or that your memory fails you?

□ Not at all
□ A little more than usual
□ More than usual
□ Much more than usual

1.5 Do you have feelings of sadness, depression, listlessness/ dispiritedness or meaninglessness?

□ Not at all
□ Somewhat more than usual
□ More than usual
□ Much more than usual

1.6 Do you feel nervous, restless, tense, or do you have trouble relaxing?

□ Not at all
□ A little more than usual
□ More than usual
□ Much more than usual

1.7 Do you sleep more, longer or heavier than usual?

□ Not at all
□ Slightly more than usual
□ More than usual
□ Much more than usual

1.8 Do you sleep less or less deeply than usual?

□ Not at all
□ A little more than usual
□ More than usual
□ Much more than usual

1.9 Are you dreaming more often or more vividly than usual?

□ Not at all
□ A little more than usual
□ More than usual
□ Much more than usual

1.10 Do you have a feeling of indifference or apathy for things happening around you?

□ Not at all
□ A little more than usual
□ More than usual
□ Much more than usual

2. Neurological signs/symptoms

2.1 Are you troubled by muscle ache, tension or cramps anywhere in your body?

□ Not at all
□ Mild, occasionally
□ Moderate, yes definitely
□ Severe, frequently

2.2 Are you troubled by stiffness/rigidity in your muscles when resting or moving?

□ Not at all
□ Mild, occasionally
□ Moderate, yes definitively
□ Severe, frequently

2.3 Are you troubled by difficulty moving, or are your movements slower/more sluggish than usual?

□ Not at all
□ A little more than usual
□ More than usual
□ Much more than usual

2.4 Are you troubled more often than usual by involuntary movements/spasms, for instance in your head and neck, face, arms, legs or upper body?

□ No, not at all
□ Yes, occasionally
□ Yes, quite often
□ Yes, almost constantly

2.5 Are you troubled more often than usual by tremors or shakings in your hands, feet or elsewhere?

□ No, not at all
□ Yes, occasionally
□ Yes, quite often
□ Yes, almost constantly

2.6 Have you noticed an increased urge to move about, to keep walking around, or

difficulty sitting still or standing still?

□ Not at all
□ I like to keep moving around, but have no difficulty sitting or standing still
□ I have to force myself to sit down or stand still
□ I have to keep walking around all the time

2.7 Have you experienced fainting spells or short blackouts, or have you had a seizure with loss of consciousness?

□ Not at all
□ Occasionally
□ On several occasions
□ Daily, one or more times each day

2.8 Do you suffer from pricking, tingling or burning sensations in your skin anywhere on your body?

□ Not at all
□ Occasionally
□ Yes, often
□ Almost all the time

2.9 Do you suffer headaches more often or more severely than usual?

□ Not at all
□ A little more than usual
□ More than usual
□ Much more than usual

3. Autonomous side effects

3.1 Have you been troubled more than usual by difficulties in focussing (blurred vision), for instance when reading, writing by hand, knitting, embroidering, working with crochet or comparable?

□ Not at all
□ Some difficulty
□ Can only read large letters, or work with larger objects

□ Cannot read or do handicraft work at all

3.2 Have you been troubled by increased salivation (mouth watering)?

□ Not at all
□ Increased salivation, but not a problem
□ Must spit often
□ Profuse salivation. I must often wipe my mouth. Pillow gets wet at night while
sleeping.

3.3 Has a dry mouth troubled you?

□ Not at all
□ A little more than usual
□ More than usual
□ Much more than usual

3.4 Have you been troubled by nausea (feeling sick) and/or vomiting?

□ Not at all
□ Some nausea
□ Severe nausea
□ Vomited on one or more occasions

3.5 Has loose stools or diarrhoea troubled you?

□ Not at all
□ A little, but not problematic
□ Need to empty my bowels frequently
□ Severe diarrhoea, difficulty keeping continence

3.6 Have you been troubled by constipation?

□ Not at all
□ A little, but not problematic
□ Constipated
□ Constipated, need to take laxatives

3.7 Have you experienced difficulties in passing your urine?

□ Not at all
□ Difficulty in beginning urination
□ The flow is weak. It takes longer than usual to empty my bladder
□ Cannot empty my bladder, need help

3.8 Do you need to urinate more frequently than normally and drink water more often
than usual?

□ Not at all
□ Yes, must urinate more often, have to get up at night
□ Yes, have to urinate several times day and night, often thirsty
□ Yes, very often, even at night, need to drink frequently

3.9 Does dizziness or fainting fits when getting up from a lying or sitting position trouble you?

□ Not at all
□ Sometimes, but I can stand up without problems
□ Must rise slowly from sitting or lying positions
□ Difficulty in standing up due to dizziness or feeling faint

3.10 Do palpitations or irregular heartbeats trouble you?

□ Not at all
□ Occasionally, not troublesome
□ Often, troublesome
□ Very often, severe problem

3.11 Does increased body sweat trouble you?

□ Not at all
□ A little more than normal
□ More than normal
□ Much more than normal

4. Other side effects

4.1 Do you have, or have you had a rash?

□ Not at all

□ Light rash on limited area
□ Rash on part of body
□ Break out all over body

4.2 Does itching trouble you?

□ Not at all
□ Light itching
□ Severe itching
□ Very severe, must scratch constantly

4.3 Have you noticed any increased sensitivity to sunlight (reddening of the skin, severe sunburn)?

□ Not at all
□ A little more than usual
□ More pronounced than usual, irritating
□ So pronounced and irritating that my medication had to be withdrawn

4.4 Have you noticed any skin discoloration (brown or other colour), localised to parts of skin exposed to light?

□ Not at all
□ Slight increase in pigmentation
□ Marked increase in pigmentation
□ So pronounced pigmentation that other people have made remarks about it

4.5 Have you gained weight during the past four weeks?

□ Not at all
□ Gained 1-2 kg
□ Gained 3-4 kg
□ Gained more than 4 kg

4.6 Have you lost weight during the past month?

□ Not at all
□ Lost 1-2 kg
□ Lost 3-4 kg
□ Lost more than 4 kg

4.9 Have you noticed milk from your nipples?

□ Not at all
□ Some
□ Yes, but not troublesome
□ Much, stains my underwear

4.10 Have you experienced tension or swelling in your breasts?

□ Not at all
□ Some tension and swelling
□ Breasts are tense and larger than normal
□ Breasts clearly enlarged

4.11 Have you experienced increased sexual interest or increased sexual desire?

□ Not at all
□ Somewhat more than normal
□ More than normal
□ Much more than normal

4.12 Have you experienced decreased sexual interest or decreased sexual desire?

□ Not at all
□ A little less than normal
□ Less than normal
□ Much less than normal

Females only

4.7a Have you noticed more discharge/bleeding when menstruating?

□ Not at all
□ Somewhat more than normally
□ More than normally
□ Profuse discharge/bleeding

4.7b Have you noticed discharge/bleeding between periods?

□ Not at all
□ Occasional discharge/bleeding
□ Substantial discharge/bleeding, occasionally

□ Frequent discharge/bleeding between periods

4.8 Have you noticed less discharge/bleeding when menstruating?

□ Not at all
□ Slightly less than normal
□ Less than normal
□ Menstruation has not occurred

4.15 Have you experienced difficulty in reaching orgasm?

□Not at all
□ Some difficulty
□ More difficult than normal
□ Rarely have orgasm

4.16 Do you have problems with a dry vagina during intercourse?

□ Not at all
□ Some dryness
□ More problems than normal
□ Severe problems, must use lubrication

Males only

4.13 Have you experienced difficulty in reaching erection?

□ Not at all
□ Slightly more difficult than normal
□ More difficult than normal
□ Cannot get erection

4.14a Have you experienced difficulties in ejaculation?

□ Not at all
□ Ejaculation slightly delayed
□ Ejaculation delayed
□ Cannot ejaculate

4.14b Have you experienced early (premature) ejaculation?

□ Not at all
□ Ejaculation slightly early
□ Ejaculation early
□ Spontaneous ejaculations

TO BE FILLED BY THE INVESTIGATOR :

Total SHARED score (until question 4.12) : ……/ 120

TOTAL SCORE FOR WOMEN : ……/135
TOTAL SCORE FOR MEN : ……../ 129

CONSEQUENCES:

□ No consequence
□ Reduction in daily dosage or introduction of a correcting treatment
□ Switch to another antipsychotic

DOSE-LIMITING SIDE EFFECT (if applicable) : ……..

Appendix 3- Questionnaire for the ability to consent evaluation- Mac-CAT-CR- customized for the PSYCHIC trial

The questionnaire aims at evaluating the ability of a patient to consent to study participation. When doubting about the ability to consent, this questionnaire has to be used after having read the Information and Consent document (Appendix 7) to the patient.

I- Project understanding (/18)

Trial's comprehension (/10)

"Can you tell me your understanding of what I just said?"

1- What is the purpose of the research project I described to you?
   - □ 2
   - □ 1
   - □ 0

2- How long will the research project last?
   - □ 2
   - □ 1
   - □ 0

3- Will you have a blood sample withdrawal if you agree to be in the study? *Or if no answers*: What sorts of things will be done with people who agree to be in the study?
   - □ 2
   - □ 1
   - □ 0

4- Will you have a questionnaire to fill for this study? *Or is no answers*: What else will be asked to people who agree to be in the study?
   - □ 2
   - □ 1
   - □ 0

5- Will participation in the study impact your routine daily treatment?
   - □ 2
   - □ 1
   - □ 0

The following criteria can be used to rate the answers:

2- Subject recalls the content of the item and offers a fairly clear version of it. A verbatim repetition of the interviewer's description is not required; in fact, paraphrase in the subject's own words is preferred.

1-Subject shows some recollection of the item content but describes it in a way that renders understanding uncertain, even after the interviewer has made efforts to obtain clarification from the subject. Examples include responses that could possibly indicate understanding but are too broad or vague for one to be sure (e.g. for purpose of research "They want to see what will happen"), or responses that contain some specific and correct piece of information but lack some other part of the critical content.

0-Subject : a) does not recall the content of the item, b) described it in a way that is clearly inaccurate, c) described it in a way that seriously distorts its meaning, even after the interviewer has made efforts to obtain clarification from the patient, d) offers a response that is unrelated to the question, e) unintelligible.

Benefit and risk (/6)

6- What might doctors learn about the treatment of schizophrenia if people decide to be in this research project?

□ 2
□ 1
□ 0

7- In what way might people who volunteer be better off by being in this research project?

□ 2
□ 1
□ 0

8- What uncomfortable things will have to be done to people in the study?

□ 2
□ 1
□ 0

The following criteria can be used to rate the answers:

2- Subject recalls the content of the item and offers a fairly clear version of it. A verbatim repetition of the interviewer' s description is not required; in fact, paraphrase in the subject's own words is preferred.

1-Subject shows some recollection of the item content, but describes it in a way that renders understanding uncertain, even after the interviewer has made efforts to obtain clarification from the subject. Examples include responses that could possibly indicate

understanding but are too broad or vague for one to be sure (e.g. for purpose of research "They want to see what will happen"), or responses that contain some specific and correct piece of information but lack some other part of the critical content.

0-Subject: a) does not recall the content of the item, b) described it in a way that is clearly inaccurate, c) described it in a way that seriously distorts its meaning, even after the interviewer has made efforts to obtain clarification from the patient, d) offers a response that is unrelated to the question, e) unintelligible.

Ability to withdraw (/2)

9- What will happen if a person refuses to be in the research project, or decides to stop once it begins?

□ 2: Subject recalls the content of the item and offers a fairly clear version of it. A verbatim repetition of the interviewer' s description is not required; in fact, paraphrase in the subject's own words is preferred.

□ 1: Subject shows some recollection of the item content, but describes it in a way that renders understanding uncertain, even after the interviewer has made efforts to obtain clarification from the subject. Examples include responses that could possibly indicate understanding but are too broad or vague for one to be sure (e.g. for purpose of research "They want to see what will happen"), or responses that contain some specific and correct piece of information but lack some other part of the critical content.

□ 0 : Subject: a) does not recall the content of the item, b) described it in a way that is clearly inaccurate, c) described it in a way that seriously distorts its meaning, even after the interviewer has made efforts to obtain clarification from the patient, d) offers a response that is unrelated to the question, e) unintelligible.

II- Appreciation (/2)

The purpose of this question is different from the Question 9 where it aimed at evaluating if the patient has understood that he/she can refuse to participate or leave the study once it begins. Here, the question aims at evaluating if the patient thinks that there would be a consequence on his ordinary care if he/she refuses to participate.

10- What do you believe would happen if you were to decide not to be in this study?

□ 2: Subject acknowledges that failure to participate or later withdrawal will not adversely affect him or her (in particular, in the context of a treatment setting, that subject can continue to receive ordinary care, assuming that this is the care).

□ 1: Subject is uncertain whether failure to participate or later withdrawal will adversely affect him or her; or subject believes failure to participate or later withdrawal will adversely affect him or her and has a plausible explanation for why this is the case.

□ 0 : Subject believes failure to participate or later withdrawal will adversely affect him or her and does not have a plausible explanation for why this is the case; or subject offers response that is unrelated to the question or unintelligible.

III- Expressing a choice (/2)

11- As you know, you have been invited to participate in a research project. Do you think you are more likely to want to participate or not to want to participate?

□ 2: Subject states a choice
□ 1: Subject state more than a choice, seems ambivalent
□ 0: Subject does not state a choice

IV- Reasoning (/8)

Consequential reasoning (/2)

12- You think that you are more likely to want to participate/not to participate in the study. Tell me what make you choose that option:

□ 2: Subject mentions at least two specific consequences when explaining a choice. The consequences may be related to only one or more than one alternative, including alternatives not mentioned in the disclosure.

□ 1 : Subject mentions only one specific consequence when explaining the choice.

□ 0 : Subject mentions no specific consequences when explaining the choice, even after asked directly whether there were "any more specific reasons why that choice seems best".

Comparative reasoning (/2)

13- You think that you are more likely to want to participate/not to participate in the study; Tell me what it is that makes that option better than the other:

□ 2 : Subject offers at least one statement in the form of a comparison of at least two options, with the comparison including a statement of at least one specific difference. For example: "I'd prefer not to take part in the study, because if I did I'd miss the recreation period we have each day." Comparative clause can be inferred from the subject's previous explanation, for example "which won't be the case if I decline to participate".

□ 1 : Subject makes comparison statement, but does not include a statement of a specific consequence. For example, "it will be better it I stay out of the study".

□ 0 : Subject makes no comparative statements.

Generating consequences (/2)

14- What are some ways that one benefit or one risk could affect your everyday activities if you participate in the research project?

□ 2 : Subject must give at least two reasonable everyday consequences, including at least one for each of the two inquiry questions: 1) the benefit 2) the risk

Note : *Everyday consequences must go beyond those in the disclosure, and must refer to practical everyday activities or social relationships. For example, if the study involves venipuncture, "my arm may hurt" is not sufficient; "I won't be able to play in my bowling league if my arm hurts" is sufficient.*

□ 1 : Subject gives one or more reasonable everyday consequence for one of the inquiry questions, but none for the other.

□ 0 : Subject gives no reasonable everyday consequences, even with adequate encouragement.

Logical consistency (/2)

15- A few minutes ago you told me that you favored participating/not participating in the research project. Now that we have discussed everything : do you want to participate in the study?

□ 2: Subject's final choice follows logically from the subject's own reasoning, as explained by the subject in response to the three previous questions.

□ 1: It is not clear whether the choice follows logically from the subject's own reasoning.

□ 0 : Subject's choice clearly does not follow logically from subject's own reasoning.

SCORE : ……./30

Score < 10 : the patient is not able to consent.

Reference :

MACArthur Competence Assessment Tool for Clinical Research (MacCAT-CR), Paul S. Appelbaum & Thomas Grisso, Professional Resource Press, 2001

Summary of oral presentations and posters presented at congresses

Title of the presentation	Type (poster, oral communication)	Name of the congress
Antipsychotic polypharmacy- Evolution of prescribing patterns between admission and discharge of 5 Belgian hospitals	Poster	World Congress of Psychiatry
Antipsychotics in psychiatric illness- Pharmacists'advices to detect and manage frequent adverse effects	Oral communication (workshop)	European Society of Clinical Pharmacy symposium
Characterising the evolution of inappropriate antipsychotic prescribing patterns during psychiatric hospitalisations	Oral communication	European Congress of Psychiatry (EPA 2022)
Antipsychotics deprescribing in schizophrenia: trends and associated characteristics in Belgium and Québec	Poster	ICOD (International Conference on Deprescribing)
Measuring the professional social capital of psychiatrists: adaptation and validation of the Resource Generator for Psychiatrists (RG-Psy)	Poster presentation	European Congress of Psychiatry (EPA 2023)