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## THERAPIES

### HEADING: Neuropsychopharmacology

## Towards personalized pharmacology: antipsychotics and schizophrenia

Personalized pharmacology and antipsychotics

**Louise Carton<sup>a,\*</sup>, Régis Bordet<sup>a</sup>, François Montastruc<sup>b,c</sup>, Romain Guilhaumou<sup>d</sup>**

<sup>a</sup> *Univ. Lille, Inserm, CHU Lille, UMR\_S1172, medical pharmacology department, 59045 Lille, France*

<sup>b</sup> *Department of medical and clinical pharmacology, centre of pharmacovigilance and pharmacoepidemiology, toulouse university hospital (CHU), faculty of medicine, 31000 Toulouse, France*

<sup>c</sup> *INSERM, UMR 1027 pharmacoepidemiology, assessment of drug utilization and drug safety, CIC 1426 - university Paul Sabatier Toulouse, 31000 Toulouse, France*

<sup>d</sup> *Clinical pharmacology and pharmacovigilance unit, AP-HM, 13354 Marseille, France; Aix Marseille univ, INSERM, INS Inst Neurosci Syst, 13354 Marseille, France*

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**\*Corresponding author.** Univ. Lille, Inserm, CHU Lille, UMR\_S1172, département pharmacologie médicale, UMR 1172 Lille neurosciences et cognition, faculté de médecine pole recherche, 1, place de Verdun, 59045 Lille cedex, France.

*E-mail address:* [louise.carton@univ-lille.fr](mailto:louise.carton@univ-lille.fr) ([L. Carton](#))

## **Summary**

Since the discovery of the first antipsychotic in 1952, many antipsychotic drugs have been developed, each with different pharmacokinetic and pharmacodynamic properties. The pharmacological heterogeneity of antipsychotic drugs should allow a personalized drug prescription adapted to the different clinical picture of schizophrenia. Schizophrenia is a chronic disease, during which 3 stages of pharmacological intervention can be identified: the first episode psychotic (FEP), the phase of therapeutic stabilization that can progress to situations of resistance, and the question of long-term prescription. During FEP, the choice of the first antipsychotic treatment seems to be underpinned by its safety profile in relation to the patient for whom it is prescribed, according to the adage start low and go-slow. The therapeutic stabilization phase is based on treatment optimization through a rigorous evaluation of the benefits-harm balance, with the use of tools such as personalized therapeutic drug monitoring and pharmacogenetics. Generally speaking, while some antipsychotic drugs seem to present a more favorable efficacy profile in certain situations, the differences are small, whereas the differences in safety are more important and should be considered in the first line. Individual factors such as the presence of co-morbidities, as well as previously experienced treatments must also be taken into account. Finally, the question of maintaining the prescription of antipsychotic drugs over the long term arises in view of the iatrogenic risk with controversial current data. Overall, the personalized prescription of antipsychotic drugs in schizophrenia remains limited by a lack of data in the literature, justifying the development of clinical studies in this field. But at present, the dogma remains that of *primum non nocere*.

## **KEYWORDS**

Personalized pharmacology; Schizophrenia; Antipsychotic; Therapeutic drug monitoring; Pharmacogenetic; Pharmacovigilance

## **Abbreviations**

ADRs: adverse drug reactions

COMT: catechol-O-methyltransferase

CYP2D6: cytochrome P450 2D6

CYP2C19: cytochrome CYP2C19

DPWG: Royal Dutch Pharmacists Association - Pharmacogenetics Working Group

DSMV: diagnostic and statistical manual of mental disorders

DUP: duration of untreated psychosis

FDA: Food and Drug Administration

FEP: first episode psychotic

FGAs: first generation antipsychotics

ICD-10: international classification of diseases 10<sup>th</sup> edition

IM: intermediate metabolizer

LAIs: long-acting injectable antipsychotics

PD: pharmacodynamic

PGx: pharmacogenetic

PK: pharmacokinetics

PM: poor metabolizer

SGAs: second generation antipsychotics

TDM: therapeutic drug monitoring

URM: ultra-rapid metabolizer poor

WFSBP: World Federation of Societies of Biological Psychiatry

## Introduction

Almost sixty years after the discovery of chlorpromazine, it is time to ask ourselves about the future in store for antipsychotics since only a few new original drugs have been put on the market in the last decade. It is now a recognized fact, since the artificial opposition between typical and atypical antipsychotics has been settled, that antipsychotics are a heterogeneous class, made up of drugs that have a common action mechanism but vary in several other dimensions. Differences between antipsychotics fall into four dimensions: (i) molecular pharmacodynamic properties; (ii) clinical pharmacodynamic properties; (iii) adverse drug reactions (ADRs) ; (iv) long-term effects [1,2]. These characteristics explain why the overall effect of each antipsychotic can be specific, and may be assessed using clinical scales, therapeutic drug monitoring (TDM), and biomarkers (imaging, neuropsychology, biology). The heterogeneity of antipsychotics opens up the possibility of using them in a personalized approach [3].

For a personalized approach to be considered, the various modalities of action of a drug class have to be counterpoised by the various clinical presentations of the treated disease. This is effectively the case in schizophrenia that is the main target of antipsychotics. Heterogeneity is observed on two levels. The first level is clinical and linked to the different symptomatic dimensions of schizophrenia that are found in various combinations in patients, resulting in different clinical profiles. The next level is time, since schizophrenia is an evolving illness, with profiles evolving differently either during the first-episode psychosis (FEP) or its long-term progression, which can take on various appearances.

Ultimately, it is when the different clinical patient profiles meet the heterogeneous pharmacological profiles of antipsychotics that the pertinence of considering a personalized therapy approach with antipsychotics arises. Three specific moments in the progression of schizophrenia and of its pharmacological approach are identified as being particularly interesting for initiating personalized therapy, combining the dimensions of illness heterogeneity and the class of antipsychotics: (i) the FEP and the identification of criteria to decide which antipsychotic to be given first, an essential step in the therapeutic alliance [2]; (ii) the therapy stabilization phase that addresses the issue of seeking the optimal response with a first-line antipsychotic but also any subsequent resistance to this pharmacological treatment [4]; (iii) long-term schizophrenia therapy, with its various evolving profiles, that raises the question of potentially stopping treatment for

favorable forms of progression, with a positive prognosis for illness progression or, on the contrary, for negative consequences either of the illness itself or of the treatment [5].

### **Schizophrenia, a heterogeneous disease**

The need for personalized therapy taking the example of antipsychotics is highlighted by the heterogeneity of the illness itself. Schizophrenia is a chronic psychotic disorder, characterized by an altered contact with reality. It can have a multitude of more or less associated symptoms and various types of progression, from total remission to severe disabilities [6]. Four symptomatic dimensions are described: positive, negative, disorganized and cognitive. Positive symptoms include delusions/hallucinations. Negative symptoms are characterized by five dimensions: anhedonia, social withdrawal, blunted affect, avolition (reduced initiative and goal-directed activity) and alogia (reduced quantity of speech). Disorganization is characterized by the loss of association between emotions, cognition and behavior. Concerning the cognitive dimension, the most impaired fields are executive functions, episodic verbal memory, concentrated attention and information processing speed [7]. Clinical presentations with various combinations of these symptoms have historically led to the definition of subtypes of schizophrenia. If these subtypes no longer appear in the fifth version of diagnostic and statistical manual of mental disorders (DSM-V) in order to privilege a dimensional approach that takes into account the heterogeneity of the different forms, the tenth version of the international classification of diseases (ICD-10) still identifies 7 groups of symptoms. These groups are: paranoid (predominance of reality distortion), hebephrenic (predominance of affect disorders), catatonic (predominance of psychomotor disorders), undifferentiated (with no specific predominant symptoms), residual (predominance of negative symptoms), simple and post-schizophrenic depression [8].

### **Antipsychotics, a heterogeneous class of drugs**

The main action mechanism of antipsychotics was under debate for a long time, with the opposition of first- and second-generation antipsychotics (FGAs and SGAs respectively) and when trying to explain observed atypia via the pharmacological response to certain molecules. Nowadays, it is agreed that the main mechanism of action of antipsychotics is to block the dopamine D2 receptor, as suggested in studies showing a correlation between the occupancy of this receptor and symptom improvement, at least for productive symptoms [9]. The modulation of this dopamine D2 receptor is not however univocal [10]. If most antipsychotics are D2 receptor antagonists, some are inverse agonists and one of them (aripiprazole) is a partial agonist. Among the antagonists, there are differences associated with the speed of dissociation between the antipsychotic and the D2 receptor, or the antagonist-receptor binding time, and these explain the differences in spatial distribution of antipsychotic binding within cerebral regions, visualized via metabolic imaging or via the duration of the antipsychotic effect.

As well as their action on the dopamine D2 receptor, antipsychotics induce multiple and varied modulations, agonist or antagonist, of the receptor systems for different neurotransmitters [11, 12] [13, 14] (Table 1). For dopamine, some are D1 or D4 receptor antagonists, while others are partial agonists (aripiprazole) or antagonists (amisulpride, risperidone) of the D3 receptor. There is a wide diversity of action on serotonergic receptors: a large number of antipsychotics are also 5HT2A receptor antagonists, there are fewer 5HT2B or 5HT2C receptor antagonists, while others (aripiprazole, clozapine, haloperidol, quetiapine) are 5HT1A receptor agonists [15]. Antipsychotics have very different actions on other neurotransmitter systems, such as acetylcholine, noradrenaline and glutamate. In this context, it is also important to take into account the genetically determined polymorphism of the D2, D3, and 5HT2A receptors, of catechol-O-methyltransferase (COMT) or of the dopamine transporter, which can increase the differential complexity of action of antipsychotics [16].

Neurotransmitters being responsible for different psychobehavioral and cognitive properties, it is therefore understandable that different pharmacodynamic receptor profiles result in different clinical pharmacodynamic properties or ADRs [1, 10]. This is notably the case for negative or cognitive symptoms. Antipsychotics such as olanzapine or clozapine, act preferentially on the prefrontal lobe and improve negative symptoms. A 5HT1A receptor agonist can have a positive or less harmful effect on cognitive symptoms. With regards to ADRs, pharmacodynamic/pharmacoepidemiological correlations showed that a 5HT2A receptor antagonist effect was associated with a lower risk of extrapyramidal effects and that histamine H1 receptor affinities were associated with a risk of weight gain [17]. Additional properties targeting oxidative

processes, neurotrophic factors, molecular components of the neuronal cytoskeleton, and neurogenesis have been described in a very variable manner from one antipsychotic to another and could represent a source of variability in long-term effects, to be used according to the predicted profile of prognosis for each patient [18]. However, the profile of each antipsychotic must be considered in its totality, as a positive effect due to the modulation of one receptor may be counteracted by another property. The 5HT1A receptor agonist effect of haloperidol is without doubt dampened by its anti-muscarinic effect, explaining why haloperidol can make some cognitive functions worse. The patient's genetic polymorphism of receptors or metabolic systems, especially hepatic, must also be confronted with the pharmacodynamic profile of each antipsychotic, in order to provide personalized therapy. For a given patient, and at each phase of the therapy, the choice of antipsychotic must take into consideration all four dimensions of the pharmacological profile: (i) pharmacodynamic profile; (ii) clinical profile; (iii) profile of ADRs; (iv) profile of long-term effects.

### **Choice of the first antipsychotic during the FEP**

#### **FEP and general principles of care**

The FEP is characterized by manifest psychotic symptoms (delusions, hallucinations, disorganization) evolving for more than 7 days [19]. It does not, as such, have its own nosological category and it may evolve towards remission, to a schizophrenic disorder or towards another psychiatric disorder (bipolar disorder). Therapy during the FEP must be treated as relatively urgent, as the duration of untreated psychosis (DUP) represents a factor of poor prognosis. Several particularities should be considered for these patients and condition the methods of care. First of all, patients are usually young and psychotic treatment-naive. This is why the first experience of psychotic drug therapy has a long-term impact in terms of therapy alliance and compliance. In terms of efficacy, patients presenting a FEP will respond to low doses of antipsychotics, and symptoms usually improve more quickly than for patients suffering from chronic illness [20, 21]. In terms of safety, these individuals are also more sensitive to ADRs such as extrapyramidal syndromes, metabolic effects and weight gain [20]. This is why treatment must be started at the minimal dose

and progressively increased to the lowest effective dose according to the motto “start low and go slow”.

### **How does personalized prescription fit in with choosing the first antipsychotic?**

First-line treatment is based on prescribing an antipsychotic with a favorable neurological safety profile, due to patients being more sensitive to extrapyramidal symptoms, which can compromise treatment adherence [21-24]. The most recent antipsychotics may also have a more favorable effect on cognition, even if this has not been fully proven [20]. The CAFE study that compared the use of olanzapine, quetiapine and risperidone for one year during the FEP did not show any differences between treatments in terms of response and safety rates. However there was more weight gain and metabolic disorders with olanzapine and less with risperidone [25]. In some countries such as Sweden or Denmark, olanzapine is no longer recommended as first-line treatment due to its metabolic ADRs [24]. Likewise, Australian recommendations for first-line antipsychotics are amisulpride, aripiprazole, quetiapine, risperidone and ziprasidone, but not olanzapine because of its poor safety profile regarding weight gain and metabolic syndrome [20]. The use of clozapine is under controversy. While it was previously limited, or even inexistent during FEP because of the potential severity of its ADRs [21], more recent studies suggest that it could be used earlier in order to obtain an earlier therapeutic response and to prevent the escalation of antipsychotic doses [26]. In Australian guidelines it is placed among fourth-line treatments [20].

Right from the first episode, therapy can be personalized. However, the choice of treatment will tend to be guided more by the safety profile than by different types of efficacy according to the clinical picture [27]. In terms of safety, aripiprazole is characterized by a higher risk of akathisia, agitation, anxiety and insomnia at the beginning of treatment, amisulpride gives a higher risk amenorrhoea/galactorrhoea by hyperprolactinaemia as well as dose-dependent extrapyramidal effects, quetiapine has anti-cholinergic effects, and risperidone causes dose-dependent extrapyramidal disorders [6]. While the criteria of choice remains the safety profile, these different antipsychotics have potentially different pharmacodynamic clinical properties. For example, amisulpride has a bipolar profile, aripiprazole is a dopaminergic regulator, olanzapine is a polyvalent antipsychotic with initial anxiolytic and sedative effects, quetiapine has numerous dose-dependent actions, and risperidone is polyvalent [6].

Beyond clinical or pharmacodynamic (PD) concerns, choice of the first-line antipsychotic could also take pharmacokinetics (PK) into consideration. Indeed, certain patients present an extreme metabolic profile justifying pharmacogenetic (PGx) tests being run prior to beginning any treatment. Medication that is a substrate of the affected metabolic pathway should be avoided in therapy. Early PGx testing is an important tool in personalized therapy but it seems difficult to prescribe it systematically to all new patients, given the heterogeneous level of recommendations according to the prescribed medication, the cost and time required to obtain results that can delay the start of therapy. This testing is therefore mostly carried out once a treatment has been started in specific clinical contexts (see “Pharmacogenetics of antipsychotics”).

## **Personalization of antipsychotic therapy during the therapeutic stabilization phase**

### **General principles in evaluating the treatment benefits/harms ratio**

Personalized prescription relies on two principal dimensions: first the drug’s safety, then its therapeutic effect. In the case of antipsychotics, surveillance mainly concerns metabolic and motor function risks. Other ADRs also need to be closely monitored, especially risks of cardiovascular disease, hyperprolactinemia and sexual disorders, which can be a reason for discontinuing medication in these young patients. Therapeutic compliance is a major issue in treatment response and long-acting injectable antipsychotics (LAIs) can also play a part during the FEP [6, 28]. They enable to limit antipsychotic administration to one injection every 14 or 28 days, thus ensuring an optimal exposure throughout that duration. Regular injections enable to achieve more stable long-term plasma concentrations that can reduce the risk of ADRs [21]. Nevertheless, the prescription of LAIs must be reserved to patients who have already been stabilized with the same molecule taken orally [6].

### **Optimization of treatment response**

## General points

Despite the fact that there are multiple antipsychotic treatments, caring for psychotic disorders remains complicated and approximately 30 to 50 % of patients have an insufficient response to treatments [29, 30]. Antipsychotic treatment response depends on the balance between prescribed dose/plasma concentration/central nervous system concentration/clinical effects. Throughout the process, several factors of variability have been described and can ultimately lead to treatment failure or to the occurrence of ADRs (Fig. 1).

In order to optimize the early response to treatment it is therefore necessary to optimize drug exposure. However, a very high PK variability is observed for these drugs that are mostly highly metabolized, and there are numerous factors explaining this PK variability. These can be demographic (influence of gender on clozapine PK), pathophysiological (influence of gastrointestinal diseases on absorption, liver diseases on metabolism) and environmental (enzyme induction due to tobacco, food effect) [31, 32]. A genetic origin for this variability has also been described. Indeed, the majority of antipsychotics are metabolized by the cytochromes P450 2D6 (CYP2D6) and 2C19 (CYP2C19) that have a high level of genetic polymorphism, characterized by different phenotypic profiles: poor (PM), intermediate (IM), rapid (RM) or ultra-rapid metabolizers (URM). Genetic polymorphisms can also affect the transport of these drugs across the blood-brain barrier (polymorphism of the gene *ABCB1*, coding for an efflux protein, P-gp or P-glycoprotein) or their direct effect via modified gene expression for the synthesis of receptors, transporters or enzymes that catabolize neurotransmitters. In addition to the factors previously described, antipsychotics are very often prescribed to polymedicated patients and multiple drug interactions can be observed. When these are PK interactions they have an impact on treatment exposure, and when they are PD they have a direct effect on treatment.

Two main tools are available for the optimization of antipsychotic exposure: therapeutic drug monitoring (TDM) and PGx.

## TDM for antipsychotics

Antipsychotic TDM is the adjustment of doses according to plasma concentrations. It is currently recommended for a large number of drugs and recent international guidelines have specified its use [33, 34]. Levels of evidence are defined for all antipsychotic molecules, according to the data available in literature on the PK/PD relationship and its impact on patient care. TDM is “strongly recommended” for molecules (clozapine, olanzapine, etc.) for which the benefit of TDM was shown in controlled studies. For other molecules (aripiprazole, quetiapine, etc.), TDM is “recommended”; a link between plasma drug concentrations and clinical symptoms being established without having been able to validate the impact on patient care [33] (Table 1). For these high levels of evidence, TDM is recommended early on, at the start of the treatment, in order to optimize exposure at best. For the other drugs, TDM is considered “useful” or “potentially useful” and limited to specific clinical conditions (loxapine, etc.): poor clinical response or occurrence of ADRs for standard doses, suspected non compliance, relapse etc.

#### Pharmacogenetics of antipsychotics

Pharmacogenetics is the study of the influence of genotype on the variability of response to a treatment [35]. Concerning psychotropic drugs, the most suitable analysis is testing for genetic polymorphism of CYP2D6 and CYP2C19 [36]. These tests enable the documentation of situations for which there is no clinical efficacy or there are recurrent ADRs, by identifying patients who are extreme metabolizers (poor or ultra-rapid). Current guidelines suggest to adjust the dose according to the CYP2D6 genotype and the Royal Dutch Pharmacists Association - Pharmacogenetics Working Group (DPWG) recommends adjusting the dose of risperidone to 67% of the standard dose for PM [37]. If ADRs occur despite lowering the dose, the dose should be further reduced to 50% of the standard dose. On the contrary, for URM, it is recommended to find an alternative treatment with an antipsychotic that is not or less metabolized by CYP2D6; these include amisulpride, quetiapine, olanzapine and clozapine. Concerning aripiprazole, the DPWG recommends not to exceed doses of 10 mg/day or 300 mg/month (67-75% of the maximum standard dose of aripiprazole) for PM. PGx testing for CYP2D6 and CYP2C19 metabolic pathways, and TDM seem to be complimentary, helping to understand, via a global pharmacological approach,

the origin of the variability of response in patients suffering from schizophrenia [38]. Finally these tools enable an early optimization of antipsychotic treatments and minimize therapeutic meandering.

The impact of genetic polymorphisms that modulate dopaminergic and serotonergic activities on the response to antipsychotic treatment is currently under study [36]. The main genes of interest are those coding for dopamine receptors (*DRD2*) and for serotonin receptors and transporters (*HTR2A*, *SLC6A*) [39]. However, to date, these PGx markers of the response to antipsychotic have not been clinically validated and supplementary studies are required.

## **Second-line antipsychotic treatment**

The response to first-line antipsychotic treatment must be evaluated after a sufficient lapse of time (at least 15 days). However, the lapse of time after which the administration of a new antipsychotic should be considered remains under debate, ranging from 2 to 8 weeks [20, 24], with some authors preferring an early switch.

Regarding the choice of second-line antipsychotic treatment, recent data recommend using olanzapine, risperidone or amisulpride in at least one of the first two lines of treatment [27]. A recent meta-analysis comparing data on the short-term efficacy and safety of 32 antipsychotics for patients who had suffered from several psychotic episodes of schizophrenia effectively showed that clozapine, amisulpride, zotepine, olanzapine and risperidone were significantly more efficient in generally reducing symptoms than other drugs [40]. More specifically, amisulpride, risperidone, olanzapine, paliperidone and haloperidol were significantly more efficient on positive symptoms. Clozapine, amisulpride, olanzapine and, to a lesser extent, zotepine and risperidone were more efficient on negative symptoms. Sulpiride, clozapine, amisulpride and olanzapine were associated with a significantly greater reduction of depressive symptoms [40]. Nevertheless, patients were not included in this study if they had predominant negative or depressive symptoms, so these results must be considered with caution, as the improvement of negative or depressive symptoms could result from the reduction of positive symptoms [40]. Furthermore, the safety profile of antipsychotics differed more than their efficacy. In general, FGAs were often associated with

extrapyramidal motor ADRs and an increase in prolactin levels, while numerous SGAs caused a greater weight gain and more sedation [40,41]. Thus, the antipsychotics shown to be more efficient, taking into consideration the limits stated above, were often those associated with the highest risk of ADRs, highlighting the importance of individualizing the assessment of risks and benefits when choosing antipsychotic treatment [41].

## **Drug resistance**

Some time after beginning a treatment, a high proportion of resistance to antipsychotics is observed in the population (approximately 30% of patients with schizophrenia). This is defined as the persistence of positive symptoms after trying antipsychotic treatment twice at suitable doses and durations and with maintained adherence. Resistance may occur right from the first episode or at some time during disease progression. There are several pharmacological hypotheses to explain this resistance, including the involvement of dopaminergic (hypersensitivity), glutamatergic, or serotonergic systems, but also inflammation and oxidative stress. The variability of symptoms associated with the variability of the pharmacological response is more in favor of a dysregulation of several neurotransmitter systems rather than a single pathophysiological mechanism.

Currently it is difficult to predict a patient's risk of being resistant to antipsychotics. Nevertheless, several studies have aimed to characterize predictive resistance factors and have identified certain populations at risk. Having a FEP young is a risk factor recurrently found in these studies [42]. Other risk factors are also identified: poor social integration before the onset of the illness, living in non-urban areas and drug abuse [42]. Patients with these sociodemographic characteristics are therefore at higher risk and require closer clinical follow-up. Introducing clozapine early can also be a solution. No clinical or genetic risk factor for resistance has been found yet, and this lack of data makes it difficult to personalize the prevention of antipsychotic resistance in these fields.

The pharmacokinetic side to antipsychotic resistance should also be taken into consideration, with an imbalance in exposure than can occur over time (defined as a "pseudo-resistance" by some authors, [43]). Indeed, in addition to the inter-individual variability previously

described, there are also factors of intra-individual variability. For example, tobacco smoking cessation leads to a rise in enzyme inhibition and increases the level of drug exposure. On an acute inflammatory background, the overexposure of patients correlated with ADRs [44]. The optimization of medication adherence is also determinant. This is why the use of LAIs has greatly progressed over the past few years. It is also interesting to note that personalization treatment tools previously presented also optimized treatment adherence. Effectively, in addition to the “repressive” side of checking adherence via the monitoring concentration levels, TDM and PGx tools reinforced exchanges between clinician and patient, making the patient participate in therapy follow-up and thus improving adherence to therapy.

Clozapine is considered to be the most efficient treatment for resistant schizophrenia, and this was confirmed in numerous randomized trials and meta-analyses [45,46]. However, the average delay for a first clozapine prescription is very long, estimated at 2 years [47], and it seems to be important to use it as early as possible to prevent the illness progressing to chronicity. With this in mind, prescribing clozapine in second- and no longer third-line is considered more and more often, especially for patients at risk (see above) [48]. Clozapine TDM is recommended right from the beginning of treatment, in order to optimize titration of the drug, and then at long-term to ensure optimal exposure [33].

## **Long-term management of antipsychotic prescription**

### **Contribution of pharmacoepidemiology**

The choice of antipsychotic must also be based on the long-term benefit-harms balance of these drugs. Indeed, caring for chronic schizophrenia with patients exposed to antipsychotic drugs has become long-term pharmacology. The assessment of the impact of long-term prescription by psychopharmacology research relies on pharmacoepidemiological methods [49]. Pharmacoepidemiology is real-life assessment, taking into account chronic exposure and on large populations, of medication use, risks and efficacy [50]. Pharmacoepidemiology applies epidemiological methods to medication and its pharmacological assessment. Pharmacological

studies can be observational and descriptive (studies on drug use for example) or analytical (an estimation of the association between a favorable or an ADRs and drug exposure).

## **Risks of long-term antipsychotic prescription**

### Antipsychotics and metabolic risks

The pharmacoepidemiological approach has, for example, contributed towards the documentation of metabolic risks with antipsychotics, which are a risk of gaining weight, of diabetes or of dyslipidemia, and occur after several months of exposure. Metabolic risks are higher with SGAs, notably, in descending order, with olanzapine, clozapine, risperidone and quetiapine [51]. Becoming overweight or obese can derive from the histamine H1 receptor agonist activity, hyperprolactinemia and hyperleptinemia. The action mechanism for the risk of becoming diabetic was investigated using a pharmacoepidemiological-pharmacodynamic approach [52]. This approach consisted of combining PD data with real-life prescription data, from pharmacovigilance or pharmacoepidemiological databases. One study using the worldwide database PharmacoVigilance Vigibase<sup>®</sup> revealed an association between the level of 5-HT<sub>2C</sub> and H1 receptor occupancy, and the induced risk of diabetes [53]. It would seem that the higher the level of 5-HT<sub>2C</sub> and H1 receptor occupancy, the higher the induced risk of diabetes.

### Antipsychotics and excess mortality

Since a warning in 2005 from the Food and Drug Administration (FDA) about excess mortality associated with SGAs in the elderly, pharmacoepidemiological approaches have been multiplied to investigate into this alert stemming from clinical trials [54]. Different studies showed excess mortality of patients treated with SGAs, with a higher risk during the first 4 weeks of exposure.

This risk of excessive mortality does not seem to be noticeably different between FGAs and SGAs [55]. The risk of excess mortality was also shown in children and young adults exposed to antipsychotics, yet again underlining the importance of remaining vigilant when prescribing antipsychotics to this category of the population [56].

### Other risks

Several questions remain concerning the risks of chronic exposure. For example, the cognitive effects of chronic exposure to antipsychotics in patients suffering from schizophrenia still need to be assessed. There also remains the question of deleterious effects of switching antipsychotics on the progression of illness. Recently, there was a pharmacovigilance alert following several cases being reported of exacerbation of psychiatric symptoms after a switch to aripiprazole from another antipsychotic [57,58]. The risk seems to be especially high in clinically vulnerable patients, with supersensitivity psychosis, a concept developed in the 90's by Guy Chouinard [59]. Supersensitivity psychosis would arise from a hypersensitivity of dopamine D2 receptors after a prolonged exposure to antipsychotics. During chronic exposure to dopamine D2 receptor antagonists, dopaminergic receptors would adjust to the change in dopaminergic tonus via 2 mechanisms. First, there would be a down-regulation of D2 receptors following their chronic blockage. Second, the dopamine D2 receptors still expressed would become hypersensitive to D2 agonists. Consequently, after prior exposure to an antipsychotic, a partial agonist for D2 receptors, such as aripiprazole, could theoretically exacerbate psychotic symptoms.

Finally, the risks of antipsychotic drug exposure during pregnancy have been investigated in several recently published studies [60]. The results of these studies are globally reassuring concerning risks of malformation [61]. However, some reports of malformation still need further investigation, as well as the long-term consequences on the development of children exposed to antipsychotics *in utero* [62].

## **Benefits of long-term prescription of antipsychotics: should they be deprescribed?**

While antipsychotics play a major role in long-term therapy for psychotic illnesses, guidelines and opinions differ concerning the length of time antipsychotics should be prescribed after the acute phase. The latest 2009 guidelines on schizophrenia from the American Psychiatric Association (APA) suggest an “indefinite” prescription of antipsychotics for patients who have had several episodes or 2 episodes of acute treatment failure within the last 5 years. In 2013, the World Federation of Societies of Biological Psychiatry (WFSBP) stated that patients should continue to take an antipsychotic for one year after their FEP, and those who had had several psychotic episodes should continue for 2 to 5 years. Obviously, non drug-related factors (patient’s involvement, psychosocial factors, other therapy) affecting the progression of the illness should also be considered. Opinions converge concerning patients with the highest risks of complication who should stay on antipsychotics for a long time (for life?). These are patients with repeated or serious suicide attempts, patients with aggressive or violent behavior, or patients with very frequent relapses.

In 2018, a pharmacoepidemiological study using the Finnish electronic health database studied the risk of treatment failure upon the discontinuation of antipsychotic treatment after a FEP. The study found that among the patients who had stopped taking antipsychotic treatment during the first year of treatment, approximately 40% suffered from treatment failure versus 30% in the population with continuous treatment [63]. Furthermore, the authors also showed that the longer the duration of antipsychotic treatment before discontinuation, the higher the risk was of treatment failure afterwards. This result can be explained by the supersensitivity psychosis described above. In fact, upon discontinuation of antipsychotic treatment, the raise in endogenous dopaminergic tonus would result in psychotic symptoms such as hallucinations, delusion and agitation. Several examples of this were reported for patients who suddenly stopped taking antipsychotic treatment. These clinical descriptions were criticized as it is difficult to distinguish the accountability of the drug from the underlying illness (indication bias). However, supersensitivity psychosis has also been reported for dopamine D2 receptor antagonists used as anti-emetics, such as metoclopramide, taken by patients with no psychiatric history [64].

Besides these reports of psychotic decompensation after treatment discontinuation, several studies also identified certain patients with “good prognosis schizophrenia” who showed a favorable progression of their illness when they stopped antipsychotic treatment [65]. Unfortunately, pharmacoepidemiological studies have not been able to identify the characteristics of patients who are the most susceptible to profit from antipsychotic treatment discontinuation.

On the whole, the majority of guidelines recommend indefinite antipsychotic treatment for schizophrenia, recurrent psychotic episodes or bipolar disorders based on studies showing that it can prevent relapses. However these drugs have weighty ADRs over time, which can be metabolic or cognitive. These ADRs are often the reason why patients ask to stop their treatment. The assessment of long-term benefits still remains uncertain and ultimately relies on clinical trials relatively short in terms of follow-up. Several pharmacoepidemiological studies have shown the benefits of antipsychotic treatment reduction or even discontinuation, especially on psychosocial functioning of patients [5]. Deprescribing antipsychotics for the most stable patients is based on this notion. The National Institute for Clinical Excellence (NICE) effectively encourages this practice, especially when it is at the patient’s request (NICE 2014). There are, however, several barriers up against deprescription, such as an unfavorable psychosocial environment when stopping medication, limited psychotherapeutic assistance, misconception of this reality by prescribing physicians and a lack of pharmacological training in deprescription [66].

## Conclusion

A personalized approach in treating schizophrenia with antipsychotics has become necessary given the varied profile of patients and their sensitivity towards ADRs. The pharmacological heterogeneity of antipsychotics gives the possibility of personalizing therapy. We identified 3 specific moments in schizophrenia progression for implementing this personalization. While some ideas have been put forward, published data remains relatively limited, highlighting the need for more clinical trials in this field. This literary review aimed to bring to light points that need to be considered on the pathway towards an evidence-based personalization of antipsychotic treatment.

## Disclosure of interest

Authors have no conflict of interest to declare

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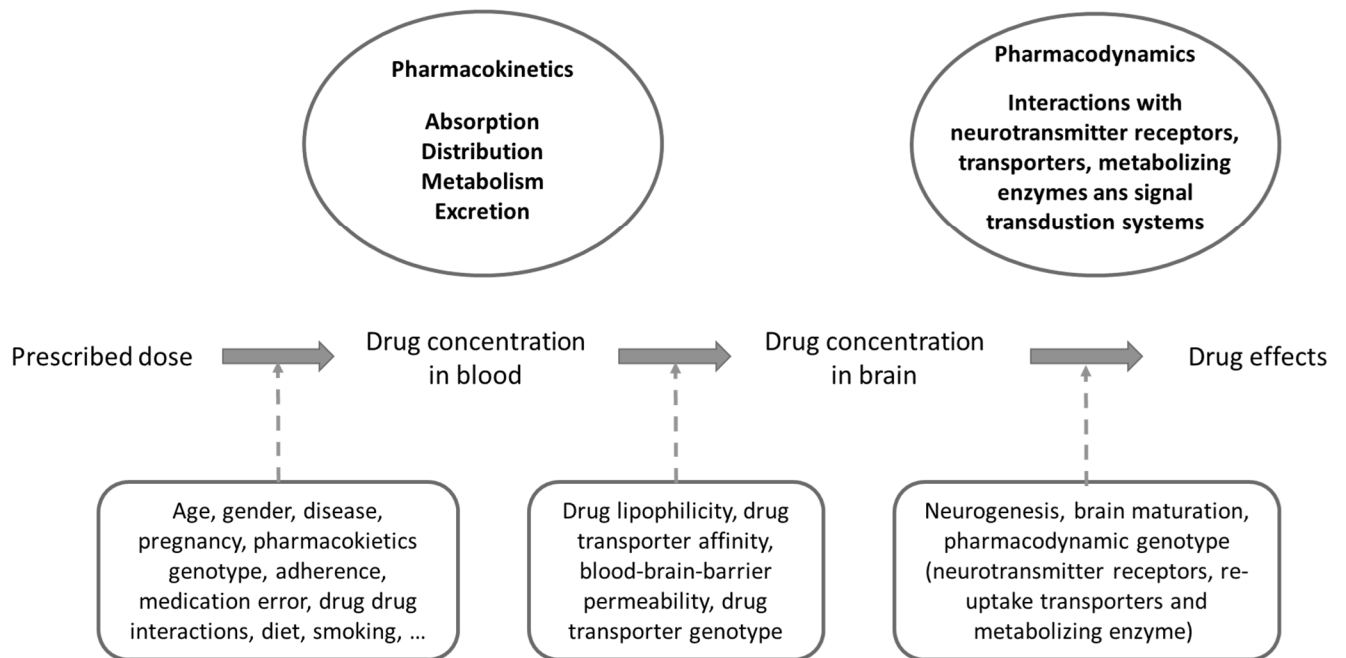
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**Figure 1.** Antipsychotics: from prescribed dose to drug effects (from Hiemke et al., 2018)

[33].



**Table 1.** Pharmacodynamic and pharmacokinetic properties of the main antipsychotics (from Hiemke et al. 2018 [33], Nguyen et al. 2017 [13], and Wierońska et al 2016 [14]).

	Main receptor targets		K <sub>i</sub> (nM) of main targets (GPCRs)			Pharmacokinetics and TDM				
	Antagonism/ reverse agonism	Full or partial agonism	Dopaminergic (D2)	Serotonergic (5HT2A)	Muscarinic (M1)	Metabolism (main enzymes involved)	f <sub>u</sub> (%)	T1/2 (h)	TDM references range (ng/ml)	TDM levels of evidence
<b>AMISULPRIDE</b>	D2, D3		12.59	8304.00	> 10000.00	More than 90 % is excreted unchanged via the kidney	84.0	12–20 h	100–320	Strongly recommended
<b>ARIPIPRAZOLE</b>	5HT2A, 5HT2B, a1, H1	D2, D3, 5HT1A, 5HT2C, 5HT7	0.79	15.85	6776.42	CYP2D6, CYP3A4	1.0	60–80 h	100–350	Recommended
<b>CLOZAPINE</b>	D1-D5, M1, M2, M3, M5	5HT1A, M4	446.68	5.01	6.59	CYP1A2, CYP2C19	5.0	12–16 h	350–600	Strongly recommended
<b>HALOPERIDOL</b>	D2, D4, 5HT2A, a1	5HT1A	7.94	100.00	> 10000.00	CYP2D6, CYP3A4	8.0	12–36 h	1–10	Strongly recommended
<b>OLANZAPINE</b>	5HT2A, 5HT2B, 5HT2C, 5HT6, a2B, a2C, M1-M5, D1- D5, H1, H2		2.09	1.78	11.38	UGT1A4, CYP1A2	7.0	30–60 h	20–80	Strongly recommended
<b>QUETIAPINE</b>	D2-D4, 5HT2A, 5HT2C, 5HT7, a1, a2, H1	5HT1A	63.10	199.53	240.44	CYP3A4	17.0	6–11 h	100–500	Recommended
<b>RISPERIDONE</b>	5HT1B, 5HT2A, 5HT2B, 5HT2C, 5HT6, 5HT7, D2, D3, D4, a1A, a1B, a2A, a2C, H1		0.44	0.22	> 10000.00	CYP2D6	11.0	2–4 h	20–60 (plus 9-hydroxy- risperidone)	Recommended

CYP: cytochrome P450; f<sub>u</sub>: free fraction of a drug in plasma; K<sub>i</sub>: equilibrium dissociation constant; TDM: therapeutic drug monitoring; UGT: UDP-glucuronosyltransferase;