

## UDPATE ARTICLE

# Animal models for predicting the efficacy and side effects of antipsychotic drugs

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The use of antipsychotic drugs represents an important approach for the treatment of schizophrenia. However, their efficacy is limited to certain symptoms of this disorder, and they induce serious side effects. As a result, there is a strong demand for the development of new drugs, which depends on reliable animal models for pharmacological characterization. The present review discusses the face, construct, and predictive validity of classical animal models for studying the efficacy and side effects of compounds for the treatment of schizophrenia. These models are based on the properties of antipsychotics to impair the conditioned avoidance response and reverse certain behavioral changes induced by psychotomimetic drugs, such as stereotypies, hyperlocomotion, and deficit in prepulse inhibition of the startle response. Other tests, which are not specific to schizophrenia, may predict drug effects on negative and cognitive symptoms, such as deficits in social interaction and memory impairment. Regarding motor side effects, the catalepsy test predicts the liability of a drug to induce Parkinson-like syndrome, whereas vacuous chewing movements predict the liability to induce dyskinesia after chronic treatment. Despite certain limitations, these models may contribute to the development of more safe and efficacious antipsychotic drugs.

**Keywords:** Antipsychotics; schizophrenia; animal models; pharmacology

## Introduction

Schizophrenia is a debilitating psychiatric syndrome afflicting approximately 1% of the world population.<sup>1</sup> Considering its psychopathological and behavioral features, the manifestations of schizophrenia have been divided into groups of symptoms, consisting of the positive, negative and cognitive types.<sup>2,3</sup> Positive symptoms include psychoses, manifesting as delusion and hallucinations, as well as paranoia, agitation and hyperactivity. The negative symptoms comprise social withdrawal, affective flattening, and lack of motivation. Finally, the cognitive symptoms comprise deficits in learning, memory, attention, and executive functions.<sup>2,3</sup> Despite recent advances in the understanding of the neurobiology and pathophysiology of this syndrome, most patients still have a poor prognosis.

The treatment of schizophrenia is largely based on pharmacological interventions with antipsychotic drugs, which were introduced in the clinics after serendipitous observations with chlorpromazine, around 60 years ago.<sup>3-5</sup> The main mechanism accounting for their clinical efficacy is an attenuation in dopamine-mediated neurotransmission, through either antagonism or partial agonism at the

D2 dopamine receptor.<sup>6</sup> Unfortunately, the efficacy of these drugs is limited to certain symptoms of schizophrenia and their use is associated with serious side effects.<sup>3-5</sup> More specifically, first-generation antipsychotic drugs, such as chlorpromazine and haloperidol, are efficacious mainly against positive symptoms.<sup>7</sup> Moreover, dopaminergic blockade leads to motor or extrapyramidal side effects, which in the short term are characterized by motor alterations similar to those observed in Parkinson's disease (bradykinesia, tremors, muscle rigidity, and postural instability), whereas long-term treatment leads to tardive dyskinesia, aberrant and involuntary movements. Other side effects related to dopamine inhibition include akathisia, dystonias, and galactorrhea.<sup>7</sup> Clozapine, olanzapine, quetiapine, risperidone, aripiprazole, and other so-called second-generation compounds or atypical antipsychotics, are considered less likely to induce such side effects. Nonetheless, they may increase body weight, trigger diabetes, and are associated with sedation, seizures, and other undesirable effects.<sup>8</sup> Most of these compounds also have limited efficacy against negative and cognitive symptoms, and, in fact, the usefulness of the concept of typical vs. atypical antipsychotics has been called into question.<sup>8,9</sup> Considering these limitations, improved pharmacological therapies are urgently required.

Basic research in laboratory animals constitutes a fruitful approach for study of the behavioral disturbances relevant to mental disorders and identification of novel pharmacological treatments.<sup>5,10</sup> Animal models must, however, fulfill some criteria of validity, of which those

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considered to be the most important are construct, face, and predictive validities.<sup>11-13</sup> Construct validity refers to how the model mimics the neurobiological mechanism of the disorder. Face validity, on the other hand, concerns the similarity between the behavioral changes observed in the model and those observed in the disease. Finally, predictive validity refers to how specific and sensitive the model is to detect pharmacological effects, avoiding false positive or false negative results.<sup>12,13</sup>

Regarding schizophrenia, the first antipsychotics (chlorpromazine and haloperidol) served as standards for characterization of the early animal models. Generally, these models consist of certain responses exhibited by rodents (mice and rats) after pharmacological, genetic or developmental interventions.<sup>10,11,14-17</sup> In this review, we focus specifically on the pharmacological models and related behavioral tests relevant for the study of schizophrenia and antipsychotic drugs. First, the pharmacological models of schizophrenia will be briefly described. Thereafter, the behavioral tests relevant for studying antipsychotic drugs will be discussed. Finally, some tests predictive of the motor side effects of these drugs will be evaluated.

### Pharmacological models of schizophrenia

Three main neurochemical hypotheses of schizophrenia have been developed, according to the effects of drugs that interfere with the neurotransmitters dopamine, glutamate, and serotonin. Drugs interfering with these systems induce certain behavioral changes in laboratory animals that can be reversed by antipsychotics. These models are briefly discussed below (see also Table 1 and Figure 1).

#### *Dopaminergic models*

As mentioned above, blockade of dopamine D2 receptors is the essential mechanism of antipsychotic drug activity, whereas dopamine-stimulating drugs can exacerbate positive symptoms in schizophrenic patients and induce psychosis-like behavior in healthy subjects. Altogether, these and other observations led to the dopamine

hypothesis of schizophrenia, which proposes that at least the positive symptoms result from excessive dopaminergic activity in the mesolimbic pathway projecting to the ventral striatum/nucleus accumbens (for reviews, see Mouri et al.<sup>19</sup> and Kapur et al.<sup>20</sup>). Several pieces of evidence corroborate this hypothesis. Recently, studies using positron emission tomography imaging indicate that there is an increase in dopamine synthesis in drug-naive schizophrenic patients as compared with age-matched controls.<sup>21,22</sup> It was also demonstrated that amphetamine induces a greater increase in dopamine release in drug-naive patients as compared with controls.<sup>23</sup>

Together, these data reinforce the role of dopamine in schizophrenia. In this way, some important experimental models used to study schizophrenia consist of quantification of behaviors in response to the administration of dopaminergic drugs, such as amphetamine, which facilitates dopamine release; cocaine, which inhibits dopamine reuptake; or apomorphine, which activates the dopamine D2 receptor directly.<sup>15,17,19</sup>

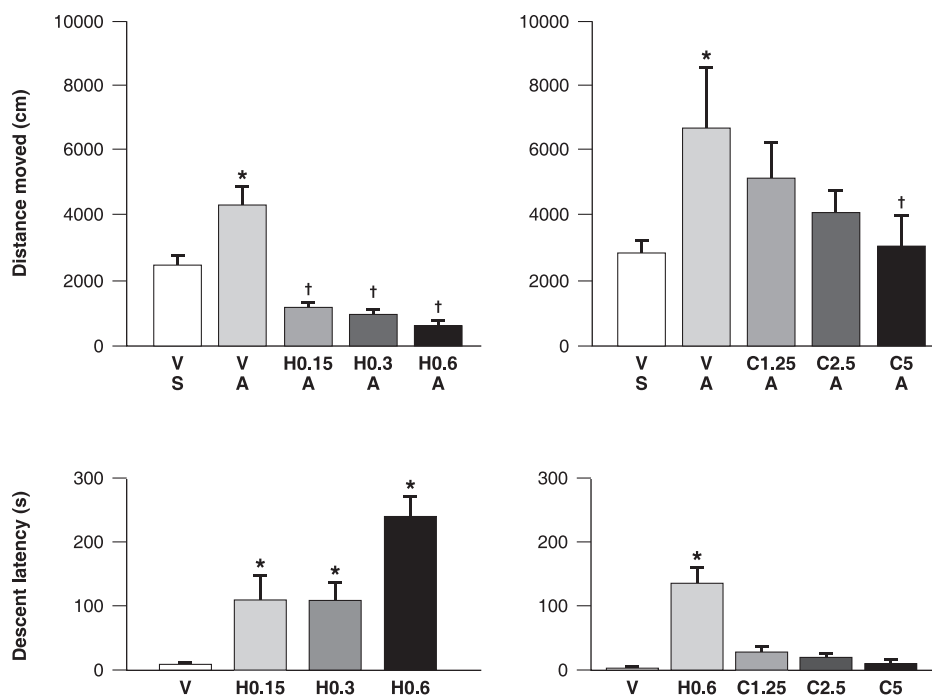
#### *Glutamatergic models*

The dopaminergic hypothesis does not provide a proper explanation for several features of schizophrenia, particularly those related to negative and cognitive symptoms. Thus, other hypotheses have emerged, focusing on a misbalance in glutamate-mediated neurotransmission. Glutamate is the major excitatory neurotransmitter in the central nervous system and exerts its actions through interaction with the ionotropic receptors for N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate, as well as with metabotropic receptors.<sup>24</sup> One important indication that glutamate may play a role in schizophrenia is a decrease in its levels in the cerebrospinal fluid of patients with this disorder.<sup>25</sup> This is in line with the fact that administration of sub-anesthetic doses of NMDA receptor antagonists, such as ketamine, phencyclidine (“angel dust”), and dizocilpine (also known as MK801), exerts psychotomimetic activity and impairs cognitive processes.<sup>5,24</sup> These effects resemble the positive and negative symptoms of schizophrenia, respectively. In addition, acute treatment with these drugs increases

**Table 1** Summary of behavioral tests, possible equivalent symptoms and pharmacological models for studying antipsychotic drugs in laboratory rodents

Behavioral tests	Symptoms of schizophrenia	Pharmacological models
Conditioned avoidance response	-	-
Stereotypies	Positive symptoms: stereotypies, agitation	Dopamine agonists NMDA antagonists
Hyperlocomotion	Positive symptoms: agitation, hyperactivity	Dopamine agonists NMDA antagonists
Disruption of prepulse inhibition of the startle reflex	Cognitive symptoms: attention deficits	Dopamine agonists NMDA antagonists 5-HT2 agonists
Reduction in social interaction	Negative symptoms: social withdrawal	NMDA antagonists
Impaired performance in the Morris water maze or object recognition test	Cognitive symptoms: learning and memory impairment	NMDA antagonists

5-HT2 = serotonin receptor type 2; NMDA = N-methyl-D-aspartate receptor.



**Figure 1** Effects of haloperidol (H, 0.15-0.6 mg/kg) and clozapine (C, 1.25-5.0 mg/kg) on amphetamine (A, 5 mg/kg)-induced hyperlocomotion (upper panels) and in the catalepsy test (lower panels) in male Swiss mice. Both drugs inhibited hyperlocomotion, whereas only haloperidol induced catalepsy, thus differentiating atypical and typical antipsychotics. The distance moved was quantified in a round arena (diameter: 40 cm) for 10 min. The catalepsy test was performed with bars elevated 4.5 cm from the bench. \*  $p < 0.05$  compared to vehicle; †  $p < 0.05$  compared to vehicle + amphetamine (ANOVA followed by the Duncan test;  $n=7$ /group). For further details, see Moreira et al.,<sup>18</sup> from which this figure has been modified.

extracellular levels of dopamine in the prefrontal cortex and alters firing patterns of dopaminergic and nucleus accumbens neurons.<sup>26,27</sup>

Therefore, an impaired glutamatergic transmission can be involved in pathophysiology of schizophrenia.<sup>24,28</sup> As with dopamine, pharmacological models based on the glutamatergic hypothesis have been established, consisting of the blockade of NMDA-receptors.<sup>26,29</sup>

#### *Serotonergic models*

The notion that serotonin might be implicated in the pathophysiology of schizophrenia is largely based on the fact that hallucinogenic substances, such as lysergic acid diethylamide (LSD), psilocybin, and mescaline, act, at least in part, through modulation of serotonin type 2 (5-HT<sub>2</sub>) receptors.<sup>30</sup> In rodents, acute or chronic treatment with these drugs induces behavioral abnormalities such as scratching, forepaw treading, head twitches, and lower lip retraction.<sup>30,31</sup> Some of these effects may depend on functional interplay between dopamine and serotonin pathways.<sup>27,31-33</sup> Indeed, some studies report that there is a decrease in the density of 5-HT<sub>2A</sub> receptors in the prefrontal cortex of patients, while there was a significant increase in the density of dopamine D<sub>2</sub> receptors in the caudate nucleus, suggesting that dysfunction in serotonergic activity could contribute to the alteration of dopaminergic function seen in schizophrenia.<sup>20,33</sup>

The discovery that the effects of some antipsychotics may be due, at least in part, to their binding to various

5-HT receptors, especially 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub>, also provides evidence that serotonin may play an important role in schizophrenia.<sup>34</sup> In this context, the serotonergic models of schizophrenia are obtained by injection of direct agonists, such as the hallucinogen DOI (a substance that resembles LSD) or serotonin-releasing agents, such as MDMA.<sup>10,14</sup>

#### **Tests that predict the efficacy of antipsychotic drugs**

The detection of antipsychotic activity in laboratory animals consists on evaluating whether a drug is able to prevent or reverse certain behavioral alterations, which can be induced by the pharmacological agents described above. Particularly relevant are the conditioned avoidance response (CAR), stereotypies, hyperlocomotion, and disruption in the prepulse inhibition of the startle reflex (PPI). Tests predictive of efficacy against the negative and cognitive symptoms will also be briefly discussed.

##### *Conditioned avoidance response*

Contrary to the other behavioral responses discussed in this review, the CAR does not require further pharmacological intervention to induce a behavioral abnormality (i.e., it is not a pharmacological model). This is one of the oldest and most classical tests predictive of the

therapeutic effects of antipsychotics agents.<sup>35</sup> In the CAR, animals are trained to avoid the occurrence of an aversive stimulation, usually an electric shock, by making a specific behavioral response in a shuttle box, such as moving to the other side of the box.<sup>10,36</sup>

Antipsychotics block the CAR in doses that do not interfere with escape after stimulus onset and correlate well with clinically used doses.<sup>35</sup> Interestingly, the percentage of striatal D2 receptor occupation required to inhibit the CAR is around 70%, similar to the threshold required for the therapeutic effect of antipsychotics in humans.<sup>35,37-40</sup> In addition, this paradigm does not tend to yield false-positive results with sedative drugs (e.g., benzodiazepines), since these normally impair both the avoidance and the escape responses. Regarding its predictive validity, this model is reliable for identifying new drugs, in addition to being simple, quick, and low-cost.<sup>35</sup> Its face validity, however, is low.

### *Stereotypies*

Stereotypy, a distinct feature of schizophrenia, is characterized by repetitive, unvarying, and functionless behavior. More recently, stereotypy has been defined as comprising strictly repetitive motor actions, thus distinguishing it from perseveration, a cognitive behavior.<sup>41</sup> It can be induced in rats and manifests as licking of the paws as well as smelling and biting the cage bars, which are part of the normal behavior of this species. These responses can be induced by direct (apomorphine) and indirect (amphetamine) dopaminergic agonists. They seem to result from the stimulation of D2 receptors located in the dorsal striatum rather than in the nucleus accumbens, the supposed site for the therapeutic activity of antipsychotic drugs.<sup>14</sup>

Various typical and atypical antipsychotics inhibit apomorphine- and amphetamine-induced stereotypies, although clozapine has been found less effective against this alteration, reflecting its supposed preferential action on D2 receptors in the limbic system, as compared to the dorsal striatum.<sup>42</sup> NMDA receptor antagonists also produce stereotypies, and the disturbance produced by these compounds, whether acutely or chronically administered, can also be prevented by treatment with antipsychotic drugs.<sup>16,43</sup>

The advantage of this test is that stereotypies can be easily quantified by a trained observer, at minimal cost and yielding rapid results. The reversion of this behavior by antipsychotic drugs demonstrates its predictive validity. Nonetheless, the fact that this behavior seems to depend on dopaminergic action in the dorsal striatum rather than in the nucleus accumbens (the supposed site for antipsychotic drug action) indicates that its construct validity is limited.<sup>14</sup>

### *Hyperlocomotion*

The increase in locomotion induced by certain drugs in experimental animals may be representative of the positive symptoms of schizophrenia. This response

results from increased dopaminergic activity in the mesolimbic pathway projecting to the nucleus accumbens.<sup>11</sup> It can be evoked by administration of direct and indirect dopaminergic agonists<sup>14,36</sup> or NMDA receptor antagonists.<sup>5,26</sup>

As for its predictive validity, hyperlocomotion is efficaciously prevented by treatment with both typical and atypical antipsychotics.<sup>10,18,44</sup> Nonetheless, compounds that induce sedative effects per se may yield false positives. Thus, an obligatory control is testing the effects of candidate drugs on baseline spontaneous locomotion, so as to ensure that the reversal of hyperlocomotion is not secondary to a sedative property of the drug. Another problem is the lack of standardization for test duration, light intensity in the room, and size of the arena, among other parameters.

Despite these drawbacks, this test has a low cost and good reproducibility. In addition, this response is easily assessed, making it appropriate for an initial screening for new candidate antipsychotic drugs in rats and mice.<sup>14</sup> Locomotion can be quantified inside a round or square arena or open field, in which automated tracking systems enable rapid and reliable analysis of drug effects. This can be achieved by recording a normal arena with a camera coupled to computer software or by an arena equipped with light beams that quantify both horizontal and vertical movement of the animals. Typical effects of haloperidol and clozapine against amphetamine-induced hyperlocomotion, recorded by a video camera and quantified by computer software, can be seen in Figure 1.

### *Disruption of the prepulse inhibition of the startle response*

The PPI seeks to explore the information processing deficits that typically occur in patients with schizophrenia. Normally, loud unexpected stimuli elicit a typical response termed the startle reflex. However, if this sudden, intense startling stimulus (pulse) is preceded by a weaker, non-startling sensory stimulus (prepulse), the startle response is inhibited (hence, prepulse inhibition). Patients suffering from schizophrenia have a deficit in PPI, meaning that they exhibit the startle response even when the pulse is preceded by the weak stimulus.<sup>36,45,46</sup>

Treatment with direct or indirect dopamine agonists mimics information processing deficits characteristic of schizophrenia, thus impairing PPI.<sup>47</sup> This is reversed by several antipsychotics, such as clozapine, haloperidol, chlorpromazine, risperidone, and quetiapine.<sup>47,48</sup> Serotonin drugs such as DOI or MDMA are also able to induce a PPI deficit.<sup>10,36,47,49</sup> Finally, another pharmacological mechanism to disrupt PPI is the antagonism of NMDA receptors. This model, contrary to the others mentioned above, may be able to distinguish the effects promoted by atypical vs. typical antipsychotics.<sup>16,47</sup> This profile is similar to that observed after administration of NMDA receptor antagonists to humans.<sup>10,36</sup>

In humans, the startle reflex can be measured as a contraction of the skeletal and facial muscles, such as an eye-blink reflex. This phenomenon occurs consistently



across species and can be assessed in laboratory mice and rats using similar stimuli (tone presentations) and measuring the startle by placing the animal over a platform that detects its movement.<sup>45,50</sup> This test has been receiving wider attention due to its face validity. Nonetheless, it requires a more expensive apparatus (the startle box) and one must control for drug effects on the startle response itself. A specific antipsychotic effect occurs when a drug restores PPI (in the prepulse-pulse sequence) without interfering with the response to the pulse alone (which would be indicative of a motor-impairing effect).

#### *Tests relevant to the negative and cognitive symptoms of schizophrenia*

Some behavioral tests, though not specifically related to schizophrenia and antipsychotic activity, may be useful in predicting efficacy against negative symptoms. Most of them consist of detecting the reversal of certain deficits induced by sub-anesthetic doses of NMDA antagonists. One example is the social interaction test. Social interaction in rats is reduced after treatment with ketamine, phencyclidine, and dizocilpine, and restored by antipsychotics. Interesting, the data have been more consistent with atypical antipsychotics.<sup>14-17</sup> Nonetheless, this activity is not specific for this class of drugs, since anxiolytic compounds also increase social interaction in rats. In any case, this test is relevant, since current antipsychotic drugs have very limited efficacy against negative symptoms.

Likewise, cognitive impairment, a common symptom of schizophrenia, is not improved by currently used medicines. Thus, there is an urgent need for drugs that are able to improve learning and memory deficits in this syndrome. Memory deficits can be induced by several protocols and tested in the object recognition test and the Morris water maze. Again, these tests are not specific for antipsychotic drugs, which do not consistently reverse memory deficits.<sup>14-17</sup> Other tests include those relevant to studying the attention process, such as the 5-Choice Serial Reaction Time Task.<sup>14-17</sup>

#### **Tests that predict the side effects of antipsychotic drugs**

As mentioned in the introduction, the short-term side effects of first-generation antipsychotic drugs include parkinsonian syndrome, dystonia and akathisia, whereas chronic treatment leads to tardive dyskinesia, which comprises abnormal, excessive, and involuntary movements.<sup>51</sup> Despite a large number of investigations, the mechanisms through which these effects occur remain to be elucidated. These include dopaminergic supersensitivity, excitotoxicity, free radical formation, and a decrease in dopamine transporter density.<sup>52</sup> To detect the liability of compounds to promote such side effects, as well as to understand their mechanisms, some simple behavioral tests can be reliably used (see also Table 2).

**Table 2** Summary of behavioral tests and possible equivalent side effects of antipsychotic drugs in laboratory rodents

Behavioral tests	Side effects	Treatment
Catalepsy test	Parkinsonian syndrome, extrapyramidal effects	Acute
Vacuous chewing movements	Tardive dyskinesia	Chronic

#### *The catalepsy test*

Catalepsy in laboratory animals is defined as a failure to correct an externally imposed posture. The test, which is widely used, consists simply of measuring latency for the animal to remove itself from an unusual and uncomfortable posture.<sup>53</sup> The most commonly used assessment is the bar test, in which a mouse or rat is placed with its hindpaws on a bench and its forepaws on a bar elevated a few centimeters. The latency for the animal to move both forepaws from the bar, or to climb it, is then measured. The cutoff time is usually 5 minutes.<sup>53</sup> In another variant, the wire grid test, the animal is positioned on a wire grid at an angle of 50 degrees to the surface. The forelimbs are spread and the time the animal remains in this position is measured.<sup>54</sup>

The catalepsy test is frequently used in drug screening to evaluate the liability of potential antipsychotics to induce extrapyramidal side effects. Generally, the doses required to induce catalepsy occupy approximately 80% of D2 receptors in the striatum, being higher than those efficacious in models predictive of antipsychotic efficacy, which requires around 65-70% occupation.<sup>35</sup> Depending on the drug, the dose difference required to induce catalepsy and antipsychotic-like effects ranges from very small, as is the case for haloperidol, to high, as for clozapine,<sup>18,55</sup> which is in line with the clinical profile of these drugs. Indeed, the doses required for antipsychotic drugs to induce catalepsy in animal correlates well with those that induce extrapyramidal side effects in humans.<sup>55</sup> Thus, this test has a very high predictive validity; it is cheap, simple, reproducible, and easy to perform.<sup>53,54</sup> Factors such as the height of the bar as well as the size of the animal must be well documented.<sup>53,54</sup> Typical effects of haloperidol and clozapine on the catalepsy test can be seen in Figure 1.

#### *The vacuous chewing movements test*

One of the most concerning side effects of antipsychotics is tardive dyskinesia, which is clinically relevant due to its high prevalence, its impact on quality of life, and the fact that it persists even after treatment discontinuation.<sup>56-58</sup> The most widely used and accepted test for studying this side effect is carried out in rats, in which the main parameter evaluated is the presence of orofacial dyskinesias, which manifest as vacuous chewing movements (VCMs).<sup>59</sup> The test is conducted in rats because mice are smaller and have rapid movements that hinder visualization and quantification of orofacial movements.<sup>60</sup>

The validity of the VCMs is based on their similarity with tardive dyskinesia in humans, since the symptoms persist chronically, can fluctuate, and continue after prolonged drug withdrawal.<sup>61</sup> Finally, not all animals exposed to long-term antipsychotic treatment develop VCMs; their incidence is higher with advancing age and symptoms is exacerbated by stress, which is also consistent with clinical observations in humans.<sup>62,63</sup>

Usually, animals are treated with slow-releasing preparations of antipsychotic drugs, haloperidol and fluphenazine decanoates being most commonly used, at a dose of 1 mg/day during periods ranging from 4 to 36 weeks.<sup>64,65</sup> For the experimental evaluation, the animals are placed individually in cages with mirrors under the floor, to facilitate visualization of the mouth. After a period of adaptation, the number of VCMs is counted. A VCM is defined as single mouth opening not directed towards physical material. Total duration of facial tremors and the number of tongue protrusions are also evaluated.<sup>66</sup>

The appearance of VCMs usually occurs after 3-4 weeks of exposure to the drug (short-term VCMs). However, while long-term VCMs reflect the development of tardive dyskinesia, the short-term VCMs reflect the acute extrapyramidal side effects, and their use to evaluate tardive dyskinesia is controversial.<sup>51,67</sup>

## Conclusions

This review discussed some of the main pharmacological models of schizophrenia in laboratory rodents and their applicability in testing the effects of antipsychotic drugs. The CAR is a non-pharmacological test useful for prediction of antipsychotic activity. In addition, dopaminergic agonists, glutamate NMDA receptor antagonists, and serotonin 5-HT<sub>2</sub> receptor agonists, which mimic psychosis in humans, induce specific behavioral changes in laboratory rodents. The typical tests to detect the acute or chronic effects of these drugs are stereotypies, hyperlocomotion, and deficits in PPI, all of which can be reversed by antipsychotic drugs. Finally, some tests can predict drug effects on negative and cognitive symptoms, including assessment of social interaction, the object recognition test, and the Morris water maze. Motor side-effects, these can be investigated through simple tests, such as the catalepsy test and the VCMs.

These tests can be more or less advantageous accordingly to the aim of each experiment. The ideal test should be simple, quick, inexpensive, and easily reproducible. There are, however, important limitations to each of them. In general, these tests have limited implications for the negative and cognitive symptoms of schizophrenia.<sup>68</sup> Furthermore, face and construct validity are questionable, particularly considering the growing view of schizophrenia as a complex developmental disorder. In this aspect, developmental models evaluating deficits in certain behaviors after social isolation, lesion of the ventral hippocampus, X-ray exposure, or methylazoxymethanol (MAM) injections have been proposed.<sup>17</sup> These approaches are, however, more demanding, time-consuming, and expensive. As for predictive validity, the

major concern of pharmacological models is that they may bring only "more of the same", as they are based on pathological hypotheses that were, in turn, partially based on the mechanisms of already used antipsychotic drugs, thus creating a circular argument. Finally, another concern is whether the doses tested have been representative of the therapeutic doses used in humans.<sup>69</sup>

Regarding models used in assessment of motor side effects, the catalepsy test is widely used to predict the liability of drugs to induce short-term extrapyramidal side effects, whereas the VCMs are predictive of tardive dyskinesia. They are simple, inexpensive, and reliable models with reasonable predictive validity. Other tests often employed for measuring motor impairment are distance moved in an arena and performance in the rotarod.

In 1987, reviewing animal models of schizophrenia, Iversen<sup>11</sup> identified five main approaches on which these models had been based over time. First, responses unrelated to the cardinal symptoms of schizophrenia; second, drug-induced dopamine hyperactivity; third, the search for anatomical and receptor specificity in relation to the dopamine hypothesis of schizophrenia; fourth, forebrain pathophysiology associated with positive and negative symptoms; and finally, rejection of classical antipsychotics as the only possible treatment of schizophrenia and the search for novel treatments with a reduced risk of extrapyramidal side effects.<sup>11</sup> Future models should indeed be sensitive to mechanisms not related to dopamine, including glutamate, endocannabinoids, and certain neuropeptides. They may also predict the effects of drugs on negative and cognitive symptoms. Focusing on modeling specific symptoms, rather than an entire psychiatric disorder, might be a more realistic approach.

Animal models initially played a very small role in the development of antipsychotics, since these drugs were actually discovered after serendipitous clinical observations. Nonetheless, these models have been increasingly employed in psychopharmacological research, and can be useful in the development of novel drugs with higher efficacy and fewer side effects for the treatment of schizophrenia.

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## Disclosure

The authors report no conflicts of interest.

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