Continuous versus extended antipsychotic dosing in schizophrenia: Less is more

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Abstract

Antipsychotic drugs temper psychotic symptoms by interacting with dopamine D2 receptors to reduce dopamine neurotransmission. Currently, the standard of care involves antipsychotic treatment protocols that achieve steady-state levels of medication. Maintaining patients on continuous treatment is thought to be necessary to keep them stabilised. However, continuous antipsychotic exposure increases the risk of adverse effects over time. These effects include metabolic and cardiovascular disorders, extrapyramidal complications, and dopamine receptor supersensitivity, the latter of which could potentially promote both treatment tolerance and psychosis relapse. In the present review, we describe evidence showing that continuous exposure to antipsychotic drugs can not only worsen long-term outcome, but—past acute phase treatment—it is also *unnecessary* to effectively manage schizophrenia symptoms. We also describe evidence that regular but extended dosing, allowing predictable periods of lower antipsychotic levels/D2 occupancy, is both safe and effective in patients, and it greatly reduces drug exposure overall. Studies in laboratory animals show that compared to continuous antipsychotic exposure, regular but extended dosing actually has superior antipsychotic-like efficacy, and it also substantially reduces the likelihood of both motor side effects and dopamine receptor supersensitivity. We propose that regular, but extended dosing should be considered in the long-term treatment of people with schizophrenia, because the available evidence suggests it can be just as effective as continuous treatment, while decreasing overall drug exposure and potentially reducing harmful side effects.

Key words: Antipsychotic drugs; Extended dosing; Continuous dosing; Schizophrenia

Abbreviations: LAI, long-acting injectable; PET, positron emission tomography; CATIE, Clinical Antipsychotic Trials in Intervention Effectiveness.

1. Introduction

A dogma in the treatment of schizophrenia is that maintaining steady-state levels of antipsychotic drug is necessary to effectively manage symptoms. Here we review literature that challenges this dogma. The standard of care for people with schizophrenia involves antipsychotic treatment regimens that achieve sustained antipsychotic levels, at doses typically producing greater than 65 % occupancy of striatal D2 receptors. This is effective in treating acute psychosis and in preventing relapse. However, maintaining continuous medication can do more harm than good, because it increases the incidence of deleterious effects [1]. Unwanted effects of antipsychotic medication include metabolic and cardiac complications, extrapyramidal disruptions, and dopamine receptor supersensitivity, the latter of which can both reduce antipsychotic efficacy and worsen psychosis [2–4]. This greatly impairs the health and quality of life of schizophrenia patients. We will highlight here recent studies in humans and laboratory animals that confront the idea that continuous exposure to antipsychotic drugs is necessary to maintain antipsychotic efficacy. These studies have compared antipsychotic treatment regimens that achieve sustained brain levels, to regimens achieving regular but extended antipsychotic dosing. As reviewed previously by Rem-

ington et al. [5], the evidence shows that regular but extended antipsychotic intake can be a safe and effective approach to treat schizophrenia patients. In laboratory animals, regular, extended antipsychotic dosing producing transient D2 occupancy above 65 % is actually more efficacious behaviourally than continuous dosing producing steady-state levels of D2 occupancy above 65 %, while reducing the risk of side effects. Thus, we lay out below that the temporal kinetics of treatment (*i.e.*, continuous versus regular but extended antipsychotic exposure) are decisive in predicting outcome. The frequency with which drug concentrations reach threshold levels throughout the course of treatment determines both treatment efficacy and the risk of unwanted side effects. We conclude then, that the temporal kinetics of treatment should be considered in the clinic, and that extended rather than continuous antipsychotic dosing could increase efficacy and potentially reduce side effects.

2. Maintaining continuous antipsychotic drug levels: more harm than good

Antipsychotic drugs exert their antipsychotic effect by reducing D2 receptor-mediated signalling. Evidence obtained from

Figure 1. The relationship between dopamine D2 receptor occupancy in the striatum by antipsychotic medication and clinical outcome. In the acute phase of schizophrenia treatment, most antipsychotics show therapeutic efficacy without an increased risk of extrapyramidal effects and cognitive deficits at doses that occupy 65 to 80 % of striatal D2 receptors. Clozapine and quetiapine are notable exceptions to this (see Section 3.1 in text).

brain positron emission tomography (PET) studies demonstrates that blockade of greater than 65 % of striatal dopamine D2 receptors with antipsychotic drugs increases the likelihood of a therapeutic response in the acute phase of schizophrenia treatment (Fig. 1) [6–8]. This notion has led to the conventional dosing strategy, which advocates using orally-administered or long-acting injectable (LAI) antipsychotics in dosing regimens that produce steady-state delivery of antipsychotic drugs to the brain and continuous blockade of over 65 % of dopamine D2 receptors (Figs. 2A–B). Antipsychotic drugs are also associated with many dose-dependent side effects, including extrapyramidal side effects [8], sudden cardiac death [9, 10], and cognitive impairments [11]. Among these side effects, extrapyramidal side effects and cognitive impairments occur more likely once dopamine D2 receptor blockade exceeds approximately 80 % (Fig. 1) [8, 11]. Based on these findings, the therapeutic window of 65–80 % D2 occupancy has been proposed for younger adults, and it is also used to determine dose and dosing frequency of new antipsychotic drugs. However, this therapeutic window of D2 occupancy is based on data from patients who were receiving acute phase treatment. Recent work shows that lower levels of antipsychotic-induced D2 receptor occupancy are effective during the maintenance phase of antipsychotic treatment [12–15]. Thus, therapeutic levels of D2 occupancy during the different stages of psychosis and schizophrenia must still be refined, as continuous antipsychotic treatment might not be necessary or even desirable in the maintenance phase of treatment.

2.1 Continuous antipsychotic treatment and dopamine receptor supersensitivity in schizophrenia

Conventional antipsychotic dosing strategies, which achieve steady-state antipsychotic levels, can also produce dopamine receptor supersensitivity in patients [2]. This is indicated by a rapid relapse to psychosis upon drug discontinuation or dose reduction, emergence of new or more severe symptoms of psychosis, tolerance to previously observed therapeutic effects and drug-induced movement disorders [2, 16–19]. Thus, dopamine supersensitivity can be detected through the presence of tardive dyskinesia [20] and supersensitivity psychosis [2, 21]. In line with this idea, a recent meta-analysis covering a total cohort of 5130 individuals found tardive dyskinesia to be the strongest predictor of psychosis relapse in patients with confirmed adherence to antipsychotic treatment (i.e., patients given LAI antipsychotics) [22]. The prevalence rate of dopamine supersensitivity psychosis is estimated to be 30% among schizophrenia patients, and even higher (70%) in treatment-resistant patients [23–25]. However, the nature of the relationship between antipsychotic-induced dopamine supersensitivity psychosis and treatment resistance is not yet clear, because treatment resistance is commonly observed from illness onset, before long-term antipsychotic exposure [26]. Using the presence of tardive dyskinesia to detect dopamine receptor supersensitivity, it is reported that supersensitivity psychosis could contribute to relapse in 30–40% of patients with schizophrenia [18, 27]. Some studies report no evidence of dopamine supersensitivity in schizophrenia patients withdrawn from antipsychotic treatment [28]. However, as the authors of that study noted ‘(...) because patients were treated with a LAI antipsychotic, withdrawal from antipsychotic treatment was gradual, potentially protecting patients from developing withdrawal or discontinuation symptoms.’ [28, p. e6]. Moreover, even people with no psychiatric diagnoses can develop both tardive dyskinesia and withdrawal psychosis when given chronic treatment with dopamine D2 receptor antagonists [29–31]. Thus, the available evidence supports the notion that sustained antipsychotic treatment can cause dopaminergic dysfunction and that this can manifest as tardive dyskinesia and worsening of psychosis.

2.2 Continuous antipsychotic exposure promotes treatment failure, motor side effects and dopamine receptor supersensitivity in rats

In rats, continuous antipsychotic treatment produces aversive effects that are similar to those that can be seen in antipsychotic-treated schizophrenia patients. As illustrated in Fig. 2C, some treatment regimens used in preclinical animal studies can mimic the continuous levels of antipsychotic exposure typical in schizophrenia patients. These regimens include administration of a LAI antipsychotic [32] or administration of antipsychotic drug via a surgically implanted, subcutaneous osmotic minipump [33]. Just like in humans, continuous antipsychotic treatment produces tolerance to antipsychotic-like effects in rodents. Antipsychotic-like effects are commonly evaluated in rats using two well validated tests: suppression of conditioned avoidance responding [34] and of the psychomotor activating effects of a dopamine agonist [35]. Antipsychotic medications reliably disrupt conditioned avoidance responding [36]. While it is not clear how conditioned avoidance of an aversive stimulus in rats relates to psychosis in humans [37], the conditioned avoidance responding model shows high predictive validity for antipsychotic activity [34]. As regards disruption of the psychomotor response to dopamine agonists, compounds other than antipsychotic drugs can also have this ef-

Figure 2. The relationship between antipsychotic treatment regimen and the temporal kinetics of striatal dopamine D2 receptor occupancy in humans and laboratory rats. The therapeutic range of 65–80 % is shaded in blue. In the clinic, standard treatment regimens for schizophrenia involve (A) daily oral intake of antipsychotic drugs or (B) administration of long-acting injectable antipsychotics. These dosing strategies typically achieve continuous levels of striatal D2 occupancy, above 65 %. (C) In rats, administration of antipsychotic drugs via a subcutaneously implanted osmotic minipump, or via intra-muscular administration of a long-acting injectable antipsychotic also produces continuous striatal D2 receptor occupancy above 65 %. (D) Because of their fast pharmacokinetic profile, regular oral intake of clozapine or quetiapine does not achieve continuous levels of D2 occupancy above 65 %, instead producing peaks and troughs in D2 occupancy, akin to a regular, but extended dosing protocol. (E) When rats receive antipsychotic drugs via regular, daily injection, this achieves transient D2 receptor occupancy > 65 %. In both C and E, doses can be used that achieve clinically-relevant levels of D2 occupancy (i.e., 65–80 %).

fect. Nonetheless, suppression of the psychomotor response to a dopamine agonist is a reliable and often used test to probe the antidopaminergic effects of antipsychotic drugs.

In rats receiving continuous antipsychotic treatment, the antipsychotic initially suppresses both conditioned avoidance responding and the psychomotor effects of dopamine agonists, but it loses efficacy later in treatment, even though striatal D2 occupancy remains above 65 % [38–40]. Also, just like in humans, continuous antipsychotic treatment in rats produces signs related to tardive dyskinesia (i.e. vacuous chewing movements) [32, 41]. Rats receiving continuous antipsychotic treatment also develop a dopamine supersensitive state, as can occur in some patients with schizophrenia [2, 17, 18, 23, 24, 42]. Dopamine supersensitivity in rats manifests among others as an exaggerated response to dopamine receptor stimulation. This exaggerated response is the most commonly used index of antipsychotic-induced dopamine supersensitivity in laboratory rodents. In rats, antipsychotic-induced dopamine supersensitivity produces robust sensitization to the psychomotor-activating effects of dopamine agonists, but also to their reward-enhancing effects [39, 40, 43–49]. Antipsychotic-evoked dopamine supersensitivity is often studied in otherwise neurologically intact animals, but it can also be seen in well-established animal models of schizophrenia symptoms [46]. Antipsychotic-evoked dopamine supersensitivity is also reported to render rats unresponsive to novel agents that otherwise restore electrophysiological and behavioural abnormalities in a rat model of schizophrenia-like symptoms [46]. The implication is that this could explain at least in part why new compounds fail in clinical trials involving antipsychotic-experienced schizophrenia patients [46]. Studies in rats also show that once dopamine supersensitivity has developed, it can ‘break through’ ongoing antipsychotic treatment [38–40], and this is potentially linked to both functional tolerance to antipsychotics [39, 40] and the emergence of vacuous chewing movements [32, 41].

3. Extended dosing in schizophrenia

Regular antipsychotic dosing remains the standard of care in the clinic, because this produces continuous levels of dopamine D2 receptor blockade that are thought to maximize therapeutic response in the acute treatment phase. However, different dosing schedules have been tested to reduce dose-dependent antipsychotic side effects as well as medication cost in the maintenance phase. An initial strategy involved targeted antipsychotic dosing, where antipsychotic treatment is resumed at the earliest signs of psychotic relapse following discontinuation. This dosing method has not been a success, because it increases the risk of relapse and rehospitalization compared to regular, continuous dosing [50–54]. Indeed, it is extremely difficult to effectively detect prodromal symptoms or the early signs of relapse [55, 56]. However, recent findings suggest that the long-term outcomes of targeted treatment might warrant further exploration. Wunderink et al. [57] completed an initial study comparing targeted versus maintenance treatment for 18 months, followed by a second study assessing outcome 5 years later [58]. In the initial study, targeted treatment was associated with a greater risk of relapse than maintenance treatment [57], in accordance with previous reports [50–54]. However, in the 5-year follow-up period (during which the initial treatment strategy was not necessarily maintained in each individual), patients in the initial targeted treatment group were taking lower doses of antipsychotic medications on average, and they also showed better social functioning over time relative to patients in the initial maintenance treatment group, while symptomatic remission did not differ between groups [58]. Because patients were not required to stay in their initial treatment group beyond the first 18 months, the findings suggest that perhaps some patients might benefit from targeted treatment on the long term [58].

Another approach to reduce overall drug exposure is extended, but regular antipsychotic dosing, in which antipsy-

chotic drugs are given regularly but with longer intervals than usual (e.g., every 2–3 days for oral antipsychotic drugs instead of everyday). Thereby, unlike the targeted approach, extended dosing involves regular, predictable periods of low drug exposure (i.e., < 65 % of D2 occupancy) but not drug-free periods per se. Below we lay out the evidence that extended dosing schedules producing regular but transient D2 occupancy above 65 % are as effective as conventional, continuous dosing schedules in preventing relapse.

3.1 Continuous D2 receptor blockade is not necessary to maintain clinical efficacy

Atypical antipsychotic drugs generally dissociate more rapidly from D2 receptors (i.e., have a faster k_{off}) than typicals do [59, but see 60], but atypicals are still efficacious in treating schizophrenia symptoms. This has led to the hypothesis that antipsychotic efficacy could be achieved even with extended antipsychotic dosing. Interestingly, the fast k_{off} property of atypicals could explain why they are generally less likely than typical antipsychotic drugs to produce dopamine-dependent side effects. For instance, compared to typical antipsychotics, clozapine is unlikely to produce tardive dyskinesia and can in fact improve tardive dyskinesia caused by other antipsychotic agents [61]. Other atypical antipsychotic drugs—including the D2 antagonists risperidone, olanzapine and quetiapine and the D2 partial agonist aripiprazole—are also thought to be less likely to produce tardive dyskinesia when compared to typicals [62–65]. Furthermore, preclinical studies demonstrate that dopamine supersensitivity is less pronounced and shorter lasting with atypical versus typical antipsychotic drugs [38, 40, 66, 67]. A faster k_{off} might reduce the risk of dopamine-related side effects by allowing a greater degree of endogenous dopamine neurotransmission via D2 receptors, despite presence of the antipsychotic.

Antipsychotic medications with a fast pharmacokinetic profile have also been informative in thinking about extended dosing. Indeed, clozapine and quetiapine not only have some of the fastest dissociation rates from D2 receptors amongst all antipsychotics [59], they also show a fast pharmacokinetic profile (i.e., rapid absorption and rapid elimination half-life [68, 69]), leading to peaks in D2 occupancy which then decline within hours after antipsychotic administration (Fig. 2D). Despite this more transient action, clozapine and quetiapine are still clinically efficacious. For instance, quetiapine can be taken 2–3 times per day [68, 70] and occupies 60–65 % of striatal D2 receptors 3 hours after administration, and 0–20 % after 12 hours [71]. Despite this transient exposure, the antipsychotic still improves schizophrenia symptoms [71]. Similarly, clozapine is generally taken once a day [72] and occupies ≤ 65 % of striatal D2 receptors 6–14 hours after administration (e.g., 33–65 % occupancy [6, 73, 74]). Preclinical studies also show that clozapine-induced D2 receptor occupancy declines within hours after administration. In non-human primates, clozapine (0.2–5 mg/kg, i.v.) can occupy up to 83 % of striatal D2 receptors immediately after administration, and occupancy declines to 40–60 % 5 hours later [75]. Similarly, in rats, clozapine (15 mg/kg, s.c.) occupies 60 % of striatal D2 receptors 1 hour after administration, and occupancy effectively disappears 24 hours later [33]. In summary, clozapine and quetiapine interact more loosely with D2 receptors and also possess a fast pharmacokinetic profile, and both characteristics could contribute to the lower incidence of extrapyramidal effects with these drugs relative to other antipsychotic drugs (typical or atypical), including haloperidol, chlorpromazine, sulpiride, risperidone and olanzapine [76–79].

Because continuous occupancy of D2 receptors does not

seem required to maintain antipsychotic efficacy, some studies have investigated the effects of extending the interval between oral antipsychotic doses. In a pilot study including 11 patients, Remington et al. [80] found that antipsychotic efficacy is maintained for at least 1–6 months with regular, but extended dosing (i.e., every second or third day). Later, Remington et al. [81] replicated this finding in a larger study (N = 35) comparing the efficacy of alternate-day versus daily dosing with risperidone or olanzapine in a double-blind, randomized placebo-controlled trial. They followed the patients for 6 months and found no increase in the risk of symptom exacerbation, relapse, or re-hospitalization in the extended dosing group [81]. Similarly, Takeuchi and colleagues [82] used the dataset from the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) to compare the therapeutic efficacy of once- versus twice-daily administration of perphenazine, which has a plasma half-life of 8–12 hours. They found no differences in effectiveness or side effects [82]. Although levels of antipsychotic-induced dopamine D2 receptor blockade were not measured in these studies, it would be reasonable to assume that the subjects receiving extended dosing treatment had lower levels of D2 receptor blockade at trough [see also 83]).

Previous studies with LAI antipsychotics also show that transient D2 occupancy above 65 % as well as longer intervals between treatment administrations does not compromise antipsychotic efficacy. For example, Nyberg et al. [84] demonstrated in a [^{11}C]raclopride PET study that eight stabilized outpatients with schizophrenia maintained a clinical response when administered haloperidol decanoate every 4 weeks, despite mean D2 blockade levels decreasing from 73 % (range: 60–82 %) at week 1 to 53 % (range: 20–74 %) at week 4. Another PET study led to the same conclusion where seven subjects with schizophrenia received LAI risperidone monthly, rather than bi-weekly, for one year [15]. Although more than half of subjects showed < 65 % D2 receptor blockade measured with [^{11}C]raclopride PET at trough, none relapsed over the follow-up period. In a randomized, double-blind placebo-controlled trial (N = 50), Carpenter et al. [85] found that fluphenazine decanoate is still effective when administered every 6 weeks instead of every 2 weeks, indicating that extended dosing intervals do not compromise the efficacy of LAI antipsychotics [85].

Consistent with this notion, a series of cross-sectional studies reported dopamine D2 receptor blockade estimated from antipsychotic blood concentrations among patients with clinically stable schizophrenia and found that sustained blockade of dopamine D2 receptor over 65 % may not be necessary for relapse prevention [12–14]. In these studies, estimated levels of dopamine D2 receptor blockade by antipsychotic were < 65 % at trough in approximately half of the patients [12–14]. The same group also conducted a single-blind, 52-week randomized controlled trial (N = 68), in which clinically stable patients with schizophrenia receiving risperidone or olanzapine were randomly assigned to either a continuous D2 blockade group (i.e., D2 receptor blockade of > 65 % at trough, estimated from antipsychotic blood concentrations) or a non-continuous blockade group (i.e., an estimated peak level of > 65 % with an estimated trough level of < 65 %) [86]. Twenty-six (76.5 %) subjects in the continuous blockade group and thirty-one (91.2 %) subjects in the non-continuous blockade groups completed the study. There were no significant group differences in any of the assessment scales for symptomatology or side effects. The association between peak/trough dopamine D2 receptor blockade with antipsychotic drugs, estimated from antipsychotic blood concentrations, and tardive dyskinesia was examined, using the dataset from the CATIE [87]. As a result, estimated dopamine D2 receptor blockade levels at trough

were significantly higher in subjects who developed involuntary movements during the study period ($N = 23$) than in subjects who did not ($N = 195$) ($71.7 \pm 14.4\%$ versus $64.3 \pm 19.3\%$, $p < 0.05$), with no significant group differences in the estimated peak levels of D2 receptor blockade ($75.4 \pm 8.7\%$ versus $72.1 \pm 9.9\%$, $p = 0.07$). Thus, greater dopamine D2 receptor blockade with antipsychotics at trough can also increase the risk of tardive dyskinesia.

3.2 The case with long-acting injectable antipsychotics

Evidence has consistently shown the effectiveness of LAI antipsychotics in preventing relapse in patients with schizophrenia [88]. In parallel, we do not know enough about the potential long-term disadvantages of treatment with atypical LAI antipsychotic drugs in humans. Indeed, long-term follow-up data with clinical assessments especially for side effects are critically lacking [89]. In addition, further investigations are clearly needed to determine appropriate dosing intervals of LAI antipsychotic drugs [89] and target drug concentrations [90]. In fact, LAI risperidone that is indicated for bi-weekly administration could be given monthly [15, 91], although the data are still preliminary. Because data on appropriate dosing interval is insufficient, patients must be carefully selected for treatment with LAI antipsychotics, based on patient treatment adherence and preferences [92], as well as dosing frequency of LAI treatment when it is administered. Moreover, potential biological changes such as dopamine supersensitivity due to this formulation should also be acknowledged. Indeed, as reviewed below in animal models (Section 4), compared to regular but extended dosing, continuous dosing can promote robust dopamine receptor supersensitivity. In this context, recent work shows that extended dosing of LAI antipsychotics, beyond the intervals indicated in product monographs is worth considering [15, 91]. Some studies claim that treatment with LAI antipsychotics is beneficial for patients with a history of dopamine supersensitivity psychosis [23, 93]. However, these results should be interpreted with much caution. First, the studies did not include a placebo condition and experimenters were also not blind to treatment condition [23, 93]. Second, the findings are sharply at odds with controlled animal studies showing that continuous dopamine D2 receptor blockade at clinically representative levels actually promotes dopamine supersensitivity [38, 39, 44].

Thus, clinical data suggest that continuous D2 occupancy is not required for the maintenance of antipsychotic response. New data from methodologically robust clinical trials highlight the many benefits of extended, but regular antipsychotic dosing. As discussed more in depth later (Section 6), this must now be confirmed in larger-scale, randomized controlled trials with longer follow-up periods.

4. Benefits of extended relative to continuous dosing: lessons from rats

Work in laboratory animals shows that extended dosing actually produces a superior behavioural profile relative to continuous dosing. Extended antipsychotic dosing can be modelled in rats by injecting them daily with antipsychotic drugs. As illustrated in Fig. 2E, this achieves $> 65\%$ of striatal D2 occupancy for a few hours, followed by a decline in occupancy until the next day's injection, leading to peaks and troughs in striatal D2 occupancy [33, 41, 94]. There is a vast literature on the effects of repeated antipsychotic injections in laboratory animals. In many of these studies, high and clinically unrepresentative

doses of antipsychotic drugs were used [33], and this promotes unwanted side effects [41, 95–97]. Here we focus specifically on studies where clinically relevant antipsychotic doses were used, that is doses achieving 65–80 % striatal D2 receptor occupancy at peak [33].

4.1 Continuous antipsychotic treatment loses antipsychotic-like efficacy over time, while extended treatment remains effective

As mentioned in Section 2.2, a common index of antipsychotic-like efficacy in rats is the suppression of the conditioned avoidance response to an aversive cue. In rats, both continuous and extended dosing regimens initially suppress this conditioned response, but over time continuous dosing loses efficacy whereas extended dosing actually becomes more effective (Figs. 3A–B) [37, 39, 98]. It appears then that continuous versus extended dosing promotes neuroadaptations that lead to opposite outcomes: tolerance versus sensitization to antipsychotic-like effects, respectively. Remarkably, this occurs even when a 20-fold lower dose is administered using extended dosing, such that greater efficacy is produced with lesser drug (0.5 mg/kg haloperidol for continuous treatment [39], versus 0.025–0.05 mg/kg haloperidol for extended treatment [37, 39]). Interestingly, rats previously given extended treatment still show a suppressed conditioned avoidance response on days where they do not receive an antipsychotic injection (Fig. 3B), and responding returns to control levels after repeated testing/additional drug-free days [37]. This suggests that extended antipsychotic treatment can produce persistent antipsychotic-like effects, thus reducing the need for daily drug administration.

Studies using suppression of the locomotor response to dopamine agonists as an index of antipsychotic-like efficacy also show that extended antipsychotic dosing is more efficacious than continuous dosing. As seen with the conditioned avoidance responding paradigm, both continuous and extended antipsychotic dosing initially suppress the locomotor-stimulating effects of dopamine agonists (Figs. 3C–D) [39]. This reflects the anti-dopaminergic effects of antipsychotics. However, with continued treatment, continuous dosing failed in maintaining this anti-dopaminergic effect, whereas extended dosing maintained efficacy—even though the latter involved a 10-fold lower dose (0.5 mg/kg haloperidol for continuous treatment, versus 0.05 mg/kg haloperidol for extended treatment) [39]. Thus, using two different behavioural paradigms (suppression of conditioned avoidance responding and of the locomotor response to dopamine agonists), extended antipsychotic dosing proves more effective than continuous dosing, in spite of lesser drug exposure.

4.2 Extended versus continuous antipsychotic dosing reduces the likelihood of motor side effects

Extended dosing considerably reduces the risk of motor disturbances in rats (see Figs. 3E–F). For instance, after 2 months of treatment, 33 to 54 % of rats receiving continuous haloperidol or olanzapine (at doses achieving between 65–90 % of D2 occupancy) show high levels of vacuous chewing movements (≥ 8 vacuous chewing movements/2 minutes) [41, 94]. In parallel, rats receiving similar doses but using an extended treatment approach do not develop vacuous chewing movements after 2 months of treatment, even at doses that achieve 70–90 % of D2 occupancy at peak. The temporal kinetics of treatment also interact with antipsychotic drug-type to determine outcome. At a dose achieving very high D2 occupancy ($> 95\%$)

Figure 3. In rats, continuous exposure to antipsychotic drugs promotes treatment tolerance, movement disorders and a state of dopamine receptor supersensitivity, while extended exposure becomes more efficacious over time, and also reduces the risk of both movement disorders and dopamine supersensitivity. (A) Continuous antipsychotic treatment progressively loses efficacy in the suppression of conditioned avoidance responding task (*i.e.*, rats develop tolerance to this antipsychotic effect). In contrast, (B) extended antipsychotic treatment gains efficacy over time (*i.e.*, rats develop sensitization to this antipsychotic effect) and also maintains efficacy even after treatment cessation. Similarly, (C) continuous antipsychotic treatment initially suppresses the locomotor response to dopamine agonists—indicating anti-dopaminergic efficacy—but fails over time. After discontinuation of continuous antipsychotic treatment, rats show an exaggerated psychomotor response to dopamine agonists, indicating a dopamine supersensitive state. In contrast, (D) extended antipsychotic treatment maintains anti-dopaminergic efficacy. After discontinuation of extended antipsychotic treatment, rats generally show a normal psychomotor response to dopamine agonists, indicating no dopamine supersensitivity. (E) Over time, continuous antipsychotic treatment promotes high levels of vacuous chewing movements, a sign related to tardive dyskinesia. (F) Extended antipsychotic treatment reduces the risk of vacuous chewing movements. (G) Continuous antipsychotic exposure promotes a dopamine supersensitive state that can breakthrough ongoing antipsychotic treatment, and that is fully unmasked after treatment cessation. In contrast, (H) extended antipsychotic exposure reduces the risk of dopamine supersensitivity.

at peak, extended dosing with the atypical antipsychotic olanzapine does not produce significant vacuous chewing movements in rats [94], whereas extended dosing with the typical antipsychotic haloperidol does, at least in some rats (17 %) [41]. This incidence remains lower than that seen when animals are treated continuously with haloperidol or olanzapine (33–54 %), at doses achieving lower D2 occupancy (65–90 %) [41, 94]. While preclinical studies using doses achieving > 90 % D2 occupancy are less clinically pertinent, the studies above demonstrate that extended antipsychotic administration—even with high doses—is much less likely to produce motor side effects in laboratory animals relative to continuous dosing. As additional converging evidence for this, with doses achieving 65–80 % D2 occupancy at peak, neither acute [36, 99] nor repeated [39] injections of antipsychotic produce catalepsy, another manifestation of motor impairment related to extrapyramidal effects. Thus, when antipsychotic medication disrupts dopamine neurotransmission continuously, this promotes neu-

roplastic changes that lead to motor side effects, but if disruption of dopamine neurotransmission is only transient, this can prevent such neuroplasticity.

4.3 Extended antipsychotic exposure is unlikely to promote dopamine supersensitivity

A notable added benefit of extended versus continuous antipsychotic dosing is that extended dosing reduces the risk of dopamine supersensitivity (see Figs. 3G–H). After treatment cessation, rats previously treated continuously have a significantly enhanced psychomotor response to dopamine agonists, while animals previously treated using an extended approach show either no change or a modest increase compared to antipsychotic-naïve control rats (Figs. 3C–D) [39, 43, 44, 66, 100].

In summary, continuous antipsychotic dosing promotes treatment tolerance and dopamine supersensitivity, whereas

extended dosing can gain efficacy over time and is unlikely to produce dopamine supersensitivity—all the while reducing total exposure to medication.

5. Neurobiological effects of continuous versus extended antipsychotic dosing

The neurobiological mechanisms underlying the different behavioural profiles produced by continuous versus extended antipsychotic dosing remain largely unknown, but there are at least some clues. For example, the D2 receptor is a critical target for antipsychotic efficacy [101–104], and some studies have assessed the effects of continuous versus extended antipsychotic dosing on D2 receptor number and function. In rats, continuous but not extended antipsychotic exposure increases the number of D2 receptors in the striatum [39, 105]. D2 receptors are functional and in a high affinity state for dopamine when coupled to Gi/o proteins (referred to as ‘D2^{HIGH}’). Both continuous and extended antipsychotic dosing can enhance the number of D2^{HIGH} receptors, but this effect is greatest with continuous treatment [39]. This suggests that continuous versus extended antipsychotic treatment might differentially influence D2-mediated intracellular function. In support, following chronic treatment (17 days), extended but not continuous haloperidol dosing increases mRNA levels for the immediate early gene *c-fos* in the caudate-putamen [39]. These gene effects were consistent with effects on behaviour, as extended but not continuous dosing also increased behavioural antipsychotic efficacy over time [39]. The positive correlation between *c-fos* mRNA induction and behavioural efficacy suggests that gene regulation could be a step in a cascade of intracellular events that contribute to or maintain response to antipsychotics over time [37, 39, 98]. This remains to be investigated further.

The mode of antipsychotic treatment also influences the neurobiological response to dopamine agonists. For instance, rats previously given continuous—but not extended—haloperidol dosing show enhanced d-amphetamine-induced gene regulation in the caudate-putamen, as indicated by increased mRNA levels for the immediate early genes *c-fos* and *Nur77* [43]. The nature of the relationship between the ability of continuous antipsychotic dosing to enhance d-amphetamine-induced gene regulation on the one hand and to potentiate behavioural d-amphetamine effects on the other, is not known. As further research resolves this issue, the available evidence suggests that continuous antipsychotic treatment changes the behavioural and neurobiological impact of dopamine stimulation, and that with extended treatment, these changes either do not occur or are less pronounced (Figs. 3G–H).

Lastly, continuous versus extended antipsychotic exposure exert distinct influences on neurobiological systems that modulate dopamine function indirectly, namely neurotensin. Neurotensin is a neuropeptide that can oppose dopamine effects through activation of type 1 neurotensin receptors [106]. Activation of these receptors decreases the affinity of D2 receptors for dopamine [107–109], and this is thought to involve D2 receptor internalization [110–112]. The temporal kinetics of treatment determine the effects of antipsychotic treatment on neurotensin and neurotensin receptor expression. Continuous but not extended antipsychotic treatment enhances neurotensin expression in the caudate-putamen, whereas only extended treatment increases neurotensin type 1 receptor level in the same region [100, see also 113]. Most importantly, neurotensin injected into the nucleus accumbens attenuates the locomotor response to dopamine agonists [114], and this effect is potentiated in rats with a history of continuous ver-

sus extended haloperidol dosing [100]. Because only rats exposed to continuous (versus extended) haloperidol develop a dopamine supersensitive state [39, 43, 100], the findings suggest that antipsychotic-evoked dopamine supersensitivity is accompanied by an enhanced ability of nucleus accumbens neurotensin to modulate dopamine-dependent behaviour. The implication is that in individuals with established antipsychotic-induced dopamine supersensitivity, the increased responsiveness to neurotensin can be exploited pharmacologically to reverse the expression of this supersensitivity.

6. Current limitations and future directions

Further investigations are warranted into the long-term effects of extended dosing strategies. For instance, it remains unclear whether extended antipsychotic dosing is less likely to produce side effects than continuous exposure in humans, as is the case in laboratory animals (see Section 4). It is tempting to predict that by reducing antipsychotic drug exposure, extended dosing strategies will reduce the likelihood of adverse side effects, as compared to continuous dosing. However, this still needs to be determined conclusively, because some findings suggest that merely reducing overall antipsychotic drug exposure does not necessarily reduce side effects. For instance, studies in non-human primates [115] and schizophrenia patients [116] show that intermittent antipsychotic exposure involving drug-free periods lasting months can exacerbate antipsychotic-induced movement disorders. However, extended dosing is different from this. It involves regular intervals of low drug exposure (i.e., < 65 % of D2 occupancy), rather than long drug-free periods.

Also, evidence regarding the efficacy of extended dosing strategies in humans (as described in Section 3) comes from a small number of studies. However, because the available evidence is promising, future studies should expand on the existing literature and address specific issues. First, future studies should include greater sample sizes. Second, antipsychotic efficacy and risk of adverse effects need to be assessed for longer follow-up periods. Third, the feasibility/efficacy of extended dosing strategies should be investigated with many different antipsychotic drugs, because most studies have only used risperidone or olanzapine. Fourth, extended dosing has been studied in a limited number of double-blind, randomized controlled trials so far [81, 82, 85]. Hence, the promising findings discussed in Section 3 need to be extended with more methodologically rigorous trials. Furthermore, it will be important to determine how extended antipsychotic dosing strategies influence the kinetics of D2 receptor occupancy in humans, because so far this has not been addressed or been estimated from plasma levels of antipsychotic drugs. Plasma concentrations do not always predict brain concentrations/D2 receptor occupancy by antipsychotic [83, 117]. Hence, future studies should measure dopamine D2 receptor occupancy levels directly, using brain imaging techniques. Lastly, extended dosing is unlikely a “one-size-fits-all” approach. Empirical data are needed to identify patients best suited for extended, but regular antipsychotic dosing.

There are also important limitations to the preclinical studies discussed in Section 4. First, only one type of extended dosing approach has been studied in laboratory animals, i.e., within-day transient exposure, achieved with daily antipsychotic injection (see Fig. 2D). It will be important in future work to characterize this more systematically in laboratory animals. For instance, one can reasonably predict that if D2 receptor occupancy by antipsychotic is low enough for long enough, this will compromise antidopaminergic effects over time. Second, it is not obvious what the extended dosing strategy used

in the rat studies in Section 4 might correspond to in humans, not the least of which because antipsychotic pharmacokinetics can be quite different across the two species [33, 118]. Third, it is unclear how the neuronal changes described in Section 5 contribute to the different behavioural effects of continuous versus extended antipsychotic treatment, as the studies above have generally established correlational but not causal links. Because of the clinical implications of antipsychotic-induced dopamine supersensitivity, particular effort should be devoted to identify why continuous antipsychotic exposure is more likely to produce this supersensitivity compared to extended exposure. Fourth, in parallel to dopamine supersensitivity and motor disturbances, antipsychotic treatment can produce many other deleterious effects, including cardiovascular and metabolic disorders [3, 119]. Future work should determine how extended versus continuous exposure influences the incidence of such effects. Fifth, there are important caveats in the preclinical models used to compare extended versus continuous antipsychotic treatment. For instance, we are not aware of a single study examining this in female laboratory animals, as this work has been done exclusively in males so far. This is an urgent knowledge gap to start filling, as schizophrenia and antipsychotic treatment are relevant to both women and men. Additionally, to our knowledge, the effects of extended antipsychotic exposure have been studied only in otherwise neurologically intact rodents. Using neurologically intact animals is useful to establish cause-and-effect relationships between the temporal kinetics of antipsychotic treatment and changes in brain and behaviour. However, it remains undetermined how extended versus continuous antipsychotic exposure fare in animal models of schizophrenia-like symptoms. Sixth, because extended dosing strategies have shown great promise in studies carried out on patients with schizophrenia (see Section 3), one important avenue for future research is determining the extent to which extended antipsychotic exposure can reverse the unwanted effects previously produced by continuous antipsychotic treatment. These unwanted effects would include treatment tolerance, extrapyramidal motor side-effects and dopamine supersensitivity. Lastly, the behavioural and neurochemical effects of continuous versus extended antipsychotic dosing have most often been compared using haloperidol [e.g. 39, 41, 43]. Little is known about similar effects using atypical antipsychotic drugs, and future research can address this.

7. Concluding remarks

For decades now, standard clinical practice in the management of schizophrenia symptoms has been to maintain steady-state levels of D2 receptor occupancy, because this is thought to be essential to maintain efficacy. However, continuous blockade of more than 65 % of D2 receptors promotes neuroadaptations leading to treatment failure, motor disturbances and supersensitivity to dopamine receptor stimulation. In contrast, regular but transient peaks in antipsychotic levels/D2 receptor occupancy, as can be achieved with extended dosing strategies, are sufficient to maintain treatment efficacy and also reduce the risk of motor side effects and dopamine supersensitivity. Remarkably, the superior profile of extended versus continuous dosing strategies is seen even when extended treatment achieves much lower antipsychotic drug exposure overall. Most research comparing outcome with continuous versus extended antipsychotic exposure has been in preclinical models. However, we also reviewed findings showing that in patients, extended dosing strategies are effective in preventing psychosis relapse. Moreover, extended dosing strategies hold great promise as they could reduce dose-dependent antipsychotic side effects. This prediction can be evaluated conclu-

sively in future work. Given the literature that we have discussed here, we also view with apprehensiveness the current commercial push to market continuous-release formulations, including LAI antipsychotics. Since the available clinical evidence, especially regarding safety, is still in shortage, large-scale methodologically rigorous randomized controlled trials with LAI antipsychotics, involving longer follow-up periods are clearly warranted. As such work unfolds, we propose that while continuous antipsychotic treatment might benefit some patients, at some treatment stages (and it remains to be determined exactly who these patients might be), the available evidence suggests that extended dosing strategies achieving transient peaks in antipsychotic levels are at least as efficacious as continuous dosing, while also being less harmful and therefore more ethical.

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