

University of Groningen

Dopamine D-2 up-regulation in psychosis patients after antipsychotic drug treatment

Thompson, Ilse A.; de Vries, Erik F. J.; Sommer, Iris E. C.

Published in:
Current opinion in psychiatry

DOI:
[10.1097/YCO.0000000000000598](https://doi.org/10.1097/YCO.0000000000000598)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Thompson, I. A., de Vries, E. F. J., & Sommer, I. E. C. (2020). Dopamine D-2 up-regulation in psychosis patients after antipsychotic drug treatment. *Current opinion in psychiatry*, 33(3), 200-205.
<https://doi.org/10.1097/YCO.0000000000000598>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



Dopamine D₂ up-regulation in psychosis patients after antipsychotic drug treatment

Ilse A. Thompson^a, Erik F.J. de Vries^b, and Iris E.C. Sommer^c

Purpose of review

Recently, it has been questioned whether the re-emergence of psychotic symptoms following antipsychotic discontinuation or dose reduction is attributable to underlying psychotic vulnerability or to rebound effects of chronic use of antipsychotic medication. It was repeatedly shown that relapse rates are high after discontinuation of maintenance treatment. A potential contributing factor could be the increase in density of postsynaptic dopamine D₂ receptors in the striatum and the higher affinity of D₂ receptors for dopamine after chronic blockade.

Recent findings

To date, little clinical evidence is available for the mechanisms involved in postsynaptic striatal D₂ receptor up-regulation after use of antipsychotic medication, and most knowledge comes from animal studies.

Summary

Further research is needed to investigate whether antipsychotic medication causes neuroadaptations leading to a dopamine supersensitive state in humans, how long such hypersensitive states may last and what differences exist between high and low D₂ affinity antipsychotic drugs. Further, information is needed on discontinuation schedules that provide optimal protection for relapse during hypersensitive periods.

Keywords

antipsychotic medication, dopamine D₂ up-regulation, dopamine supersensitivity psychosis, relapse

INTRODUCTION

Schizophrenia spectrum disorders are clinically characterized by positive symptoms (e.g. hallucinations and delusions), negative symptoms (e.g. motivational impairment, social withdrawal and apathy) and cognitive alterations (e.g. an inability to sustain attention and poor executive functioning). Several theories have tried to explain the onset of psychotic symptoms, of which the dopaminergic theory is the most accredited one. This theory states that a complex dopaminergic dysregulation may underlie the positive symptoms of schizophrenia [1]. Pharmacotherapy with antipsychotic medication is the standard treatment for patients who experience psychosis, according to most national and international guidelines [2,3]. All antipsychotics act downstream at the dopamine D₂ receptors on the postsynaptic terminals to reduce dopamine-mediated signaling, which reduces psychotic symptoms. Chouinard *et al.* [4] proposed that chronic use of antipsychotic medication may lead to compensatory changes and a dopamine-sensitive state. Dopamine (super)sensitivity (DSP) is the excessive response to the (natural, or amphetamine-induced)

release of dopamine. DSP is characterized by the rapid re-emergence of psychotic symptoms after discontinuation or dose reduction of antipsychotic medication, and subsequent tolerance to antipsychotic treatment and eventually refractoriness [5]. A plausible explanation for (super)sensitivity to

^aUniversity of Groningen, University Medical Center Groningen, Department of Biomedical Sciences of Cells & Systems, Section of Cognitive Neurosciences, ^bUniversity of Groningen, University Medical Center Groningen, Department of Biomedical Sciences of Cells & Systems, Section of Cognitive Neurosciences, Groningen and ^cUniversity of Groningen, University Medical Center Groningen, Department of Biomedical Sciences of Cells & Systems, Section of Cognitive Neurosciences, Groningen, the Netherlands

Correspondence to Ilse A. Thompson, MSc, University of Groningen, University Medical Center Groningen, Department of Biomedical Sciences of Cells & Systems, Cognitive Neurosciences, Groningen, the Netherlands. E-mail: i.a.thompson@umcg.nl

Curr Opin Psychiatry 2020, 33:200–205

DOI:10.1097/YCO.0000000000000598

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

KEY POINTS

- There is no clear evidence for a relationship between dopamine D₂ receptor up-regulation and dopamine supersensitivity psychosis (DSP) in schizophrenia patients;
- Risk for relapse of psychosis is high, which may be increased with prolonged exposure to antipsychotics;
- The potential mechanism behind high relapse rates, in patients who discontinue antipsychotic medication after maintenance treatment, may be D₂ receptor up-regulation;
- Further research is needed to determine whether changes in dopamine neurotransmission are present in patients after starting antipsychotic treatment.

dopamine is the up-regulation of D₂ receptor expression or an increase in the fraction of the receptors that are in the high-affinity state [4]. In the time the hypothesis was put forward, antipsychotic dosing regimen tended to be a 10–20-fold higher than now. However, this up-regulation may cause a potentially supersensitive postsynaptic receptor system, which, in combination with a presynaptic dopaminergic system not being sufficiently suppressed, may increase the risk of relapse after discontinuation. Previous studies have indicated that the risk of symptom recurrence was between 67 and 77% one year after discontinuation, and had increased to over 90% two years after discontinuation [6[■],7]. Interestingly, the former study [6[■]] also investigated whether the length of antipsychotic treatment before discontinuation associated with risk of relapse. The groups were divided into 12 months or less of antipsychotic treatment ($n = 42$), and at least 12 months treatment ($n = 20$). Interestingly, it was noted that the duration of prior antipsychotic treatment was not associated with a reduced risk of relapse. However, other studies show an increase risk of relapsing when discontinuing, as studies show that patients who do not use antipsychotic medication for a prolonged time are significantly less likely to relapse [8,9]. These figures clearly issue a warning against discontinuation of maintenance therapy, as risk for recurrence of psychosis is high, but they also indicate that recurrence rates become even higher with prolonged exposure to antipsychotics when discontinuing treatment. Thus, while it is widely assumed that a psychotic episode following antipsychotic discontinuation or dose reduction is attributable to the underlying psychotic illness, there have been concerns that discontinuation after maintenance treatment may actually make patients

more vulnerable to psychotic relapse than would be the case in the natural course of the illness without antipsychotic treatment [10]. It is important to emphasize that the validity of the DSP hypothesis, namely an up-regulation of dopamine D₂ receptors provoked by chronic and long-term occupancy of dopamine D₂ receptors, leading to an increased density of postsynaptic dopamine D₂ receptors in the striatum, has not been fully proven yet, at least not in clinical studies [11]. In this review, we will summarize the evidence for and against this hypothesis.

ANIMAL STUDIES

A possible mechanism underlying DSP may be an increased dopamine D₂ receptor density in the striatum. Several studies have shown that the chronic administration of haloperidol indeed increased the dopamine D₂ receptor density in the striatum in rodents [12[■],13–16]. The most recent study [12[■]] evaluated the effects of 21-day repeated administration of haloperidol at 1 mg/kg and brexpiprazole at 4 mg/kg on striatal dopamine D₂ receptor density in rats, and found that while haloperidol increased the density, brexpiprazole showed no effect, compared to vehicle treatment. This suggests that brexpiprazole may have a lower risk of increasing the D₂ receptor density, and possible consequently relapsing after repeated administration. A recent study indeed shows fewer relapses in brexpiprazole compared to cariprazine and lurasidone [17]. Another recent study [13] compared blonanserin at 0.78 mg/kg with haloperidol at 1.1 mg/kg twice daily for 28 days. The results showed an increased striatal dopamine D₂ receptor density in the rats treated with haloperidol, whereas blonanserin did not show an effect. This suggests that blonanserin is less likely to induce an up-regulation of the dopamine D₂ receptor density as compared to haloperidol. Furthermore, aripiprazole at 10 mg/kg has been shown to cause up-regulation of the dopamine D₂ receptor [18], although another study with a lower dose of 1.5 mg/kg did not show an up-regulation of the D₂ receptors [16]. Olanzapine at 10 mg/kg has also been shown to not increase the D₂ receptors [15].

Moreover, the study by Amada *et al.* [12[■]] reported that the chronic treatment of risperidone (1.5 mg/kg) significantly increased locomotor activity induced by apomorphine (0.1 mg/kg; $P < 0.01$), suggesting sensitized D₂ receptors in rats after the chronic treatment of risperidone. The study by Hashimoto *et al.* [13] reported significantly enhanced hyperlocomotion in rats treated with haloperidol, whereas with blonanserin, the total hyperlocomotion was not significantly different to vehicle-treated rats. This suggests that blonanserin might be less

likely to induce DSP after chronic administration, compared to haloperidol.

Another possible mechanism to underlie DSP is the increase in number of dopamine D_2^{high} receptors. It is known that dopamine D_2 receptors can exist in a state of high-affinity (G-protein-coupled high-affinity; D_2^{high}) or in a state of low-affinity for dopamine (G-protein-uncoupled low-affinity; D_2^{low}) [19]. Dopamine D_2^{high} is the functionally active state of the dopamine D_2 receptor [19]. While antipsychotic medication may not elevate the density of dopamine D_2 receptors, it has been shown that they can increase the number of dopamine D_2^{high} receptors in animal studies [20]. Although it should be noted that the animals in this study were still being treated with olanzapine when the analysis was performed, with an occupancy of approximately 70%. The study by Samaha *et al.* [21] investigated presynaptic and postsynaptic elements of the dopaminergic system during ongoing treatment by measuring the ability of haloperidol to inhibit amphetamine locomotion. They found a tolerance to increase dopamine and dopamine turnover presynaptically, while showing a 20–40% increase in D_2 receptor number postsynaptically, and 100–160% increases in the proportion of D_2^{high} postsynaptically. These results suggest that antipsychotic treatment may lose its efficacy related to dopamine D_2 receptor increase.

Another study [22] investigated whether continuous or intermittent treatment induced amphetamine-induced locomotion in rats, as an indication of antipsychotic-induced dopamine supersensitivity. Haloperidol was continuously or intermittently administered for 16–17 days. After 3–5 days, amphetamine-induced locomotion was measured. The results showed that only the rats with continuous treatment showed enhanced amphetamine-induced locomotion. It could be argued that continuous treatment with antipsychotic drugs may cause neuroadaptations, inducing supersensitive behavior, whereas intermittent dosing is not associated with such behavior [22,23]. This could be of clinical interest, as present patient guidelines recommend 1-year continuous antipsychotic treatment after an episode of psychosis. It could be argued that some patients benefit from continuous treatment, whereas it might also promote neuroadaptations that could cause dopamine supersensitivity. However, relapse rates are shown to be high after 1–2 years of treatment who are treated with depot antipsychotics (i.e. continuous treatment with high adherence).

CLINICAL STUDIES

Whereas animal studies have shown that chronic administration of antipsychotic treatment can lead

to neuroadaptations, there are very few recent clinical studies examining whether antipsychotic medication plays a role in the up-regulation of dopamine D_2 receptors in humans, and whether relapse following antipsychotic withdrawal is linked to an up-regulation of dopamine D_2 receptors. Clear evidence that chronic exposure of antipsychotic medication can lead to a ‘dopamine supersensitive state’ is lacking [24].

Clinical studies investigating the role of antipsychotic medication in neuroadaptations

The first clinical study [25] investigating the role of antipsychotic medication in the up-regulation of dopamine D_2 receptors compared patients with schizophrenia ($n=9$) who had received long-term antipsychotic treatment relative to antipsychotic-naïve patients with schizophrenia ($n=8$). Patients were treated with first-generation antipsychotics (e.g. haloperidol, perhenazine) and second-generation antipsychotics (risperidone, olanzapine) in moderate to high dosages. Fourteen days after drug withdrawal, the binding potentials of dopamine D_2 receptors were measured using positron emission tomography (PET) using [^{11}C]raclopride, a radioligand of the dopamine $D_{2/3}$ receptor antagonist. Results showed that long-term treatment with antipsychotics were associated with a substantial increase of 30% in D_2 receptor binding in the striatum. Another study [26] scanned eight antipsychotic-naïve patients with schizophrenia, using [^{11}C]-(+)-PHNO PET – a radioligand of the dopamine $D_{2/3}$ receptor antagonist, to estimate dopamine $D_{2/3}$ receptor binding in patients. Patients were scanned before treatment and after approximately 2.5 weeks of treatment of either olanzapine at 10 mg/day or risperidone at 2–3 mg/day. Results show that 40–45% of the D_2/D_3 receptors in the caudate and putamen was occupied by the therapeutic drug (i.e. less receptor availability). The authors suggest that this lower receptor availability might be due to lower doses used in first episode patients. Indeed, a small but significant elevation in D_2/D_3 receptor availability has been found in patients who use antipsychotic medication ($d=0.26$, $P=0.049$) as compared to antipsychotic-naïve patients, although this finding is not consistent across studies [27]. Moreover, when caudate and putamen in treated patients were analyzed separately, no significant differences in D_2/D_3 receptor availability were observed. Interestingly, the results of the meta-analysis show that dopamine D_2 receptor density is unaltered in drug-naïve patients before antipsychotic medication, which suggests that D_2/D_3 alterations are not intrinsic to the illness,

but may be secondary to chronic antipsychotic treatment [27]. It has been suggested that 36–39% of relapsed patients chronically treated with antipsychotic medication show dyskinesia, suggesting that these patients may be ‘supersensitive’ [28,29]. However, it should be noted that this study associated abnormal involuntary movements (i.e. dyskinesia) with D₂ hypersensitivity, but did not measure dopamine D₂ receptor availability. Contradictory to those results are the results of another study [30] that found no differences between patients discontinued after treatment with either placebo ($n=97$) or ongoing antipsychotic treatment ($n=36$) (paliperidone palmitate once monthly). This clinical study was conducted to compare the nature of relapse after either condition, in terms of onset and severity of psychotic symptoms, the presence of tardive dyskinesia and the relapse symptom profiles. Thus, the authors state that the study found no evidence for withdrawal-related phenomena contributing to high relapse rates after the discontinuation of antipsychotic medication.

Clinical studies investigating possible biomarkers for the development of dopamine supersensitivity psychosis

In a recent study [31^{*}], first episode psychosis patients ($n=25$) were compared to healthy controls ($n=14$) to investigate whether dopaminergic function changes after the discontinuation of antipsychotic medication. At baseline patients started tapering off medication, and at 4 weeks patients completed tapering off. The participants completed two [18F]FDOPA PET scans: at baseline (i.e. prediscontinuation) and after 6 weeks of treatment (i.e. 2 weeks postdiscontinuation), and a [11C]raclopride PET scan at 7 weeks. The results showed no significant difference between relapsed and nonrelapsed patients in dopamine D₂ availability, although a trend towards significance was observed ($P=0.055$). Furthermore, relapsing patients showed an increase in dopamine synthesis, compared to nonrelapsing patients. This is in line with previous research, suggesting that relapse may be associated with presynaptic abnormalities instead of with postsynaptic D₂ availability or dopamine transporters [27]. The authors suggest that relapsed patients could be different in the underlying pathophysiology [31^{*}]. Therefore, dopamine synthesis measured using PET could possibly be used for the prediction of relapse after discontinuing antipsychotic medication in a first episode of psychosis, by validating dopamine synthesis as a possible biomarker. Another recent study by Kanahara *et al.* [32] investigated the possible biomarker CYP2D6 – one of

the most important drug-metabolizing enzyme, which is suggested to be involved in dopamine supersensitivity. CYP2D6 may be a possible biomarker, as patients with an impaired allele may have higher concentrations of the antipsychotic and its active metabolite. Thirty-six patients were divided in two groups: one with normal metabolizing activity and the other with lower activity of its variant. The concentrations of risperidone and 9-OH-risperidone were measured in blood samples. The results showed that no effect of the enzyme, or metabolism on relapse could be detected. DSP may be associated with D₂^{high}, but not with the total D₂ receptor density, as an increase in D₂^{high} receptors without significant increases in dopamine D₂ receptors have been observed in an animal model by Seeman [33]. A recent study by Kubota *et al.* [34] indicated a higher proportion of D₂^{high} in the putamen of drug-naïve ($n=10$)/drug-free ($n=1$) patients with schizophrenia as compared to healthy controls, despite the total amount of dopamine D₂ receptors being unaltered. This is in line with Chouinard *et al.* [35], who proposed that the chronic use of antipsychotics may increase the total number of dopamine D₂ receptors and dopamine D₂^{high} receptors in the striatum, without showing significant changes in the presynaptic dopamine release, synthesis, or reuptake. The authors hypothesized that the increase in D₂ receptors enhances D₂-mediated dopamine signaling, which produces a state of supersensitivity to stimulation of a dopamine agonist. This could lead to DSP. However, it is not clear whether this effect is caused by antipsychotic treatment, as the studies by Kubota *et al.* [34] and Seeman [33] found, enhanced high-affinity D₂ receptor density in patient and animal models without antipsychotic treatment. To date, only a limited number of studies investigated whether alterations exist in the amount of D₂^{high} or in the proportion of D₂^{high} ligand binding in patients with schizophrenia [34], and there is no evidence yet about the effect of drug discontinuation on the affinity state of D₂ receptors. High relapse rates have been associated with antipsychotic treatment resistance [36^{***}], as it has been shown that antipsychotic dose is significantly higher in patients after a second episode of psychosis [36^{***}]. However, it could be argued that this may actually be the up-regulation of dopamine D₂ receptors, as the animal model by Samaha *et al.* [21] demonstrated a reduced efficacy after long-term administration of antipsychotic medication, which could be partly compensated by an increase in drug dose. Furthermore, the studies showed that both the concentration of D₂ receptors and the fraction of receptors in the high-affinity state were significantly increased when resistance occurred.

CONCLUSION

While it is widely assumed that the re-emergence of psychotic symptoms following antipsychotic discontinuation (or reduction) is attributable to the underlying psychotic vulnerability, relapse risk may partly be caused by receptor up-regulation after chronic antipsychotic use. There is sparse clinical evidence for dopamine supersensitivity, but stronger evidence from animal studies. Antipsychotic drugs with lower D₂ blockade, such as the partial agonist aripiprazole, lower dose and intermittent treatment, seem to reduce this risk [16]. Thus, maintenance therapy at the lowest possible dose is needed to obtain clinical stability, as risk for symptom recurrence after withdrawal is very high. When patients want to discontinue antipsychotic medication, tapering off should be performed over prolonged time (3–6 months) and under regular supervision. A previous study showed that in FEP patients this was feasible in only 20% [37]. Because antipsychotic medication is the mainstay of treatment in psychosis, a greater understanding of dopamine up-regulation and its prevention may greatly affect patient outcomes. To date, little clinical evidence is available for the mechanisms involved in postsynaptic striatal D₂ receptor up-regulation and the influence of antipsychotic medication. Therefore, new clinical studies are needed to investigate whether changes in dopamine neurotransmission are present in (drug-naïve) patients after starting antipsychotic treatment.

Acknowledgements

None.

Financial support and sponsorship

Disclosure of funding received for this work from an organisation: Zonmw Large Trial GGG ("HAMLETT"), 80-84800-98-41015.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III: the final common pathway. *Schizophr Bull* 2009; 35:549–562.
2. National Collaborating Centre for Mental Health UK. Psychosis and schizophrenia in adults. In: *Psychosis and Schizophrenia in Adults: Treatment and Management: Updated Edition 2014*. National Institute for Health and Care Excellence (UK). <https://www.nice.org.uk/guidance/cg178>. Accessed 8 January 2020.
3. Early Psychosis Guidelines Writing Group. Australian Clinical Guidelines for Early Psychosis. A Brief Summary for Practitioners. 2nd ed. Melbourne: Orygen Youth Health; 2010.
4. Chouinard G, Jones BD, Annable L. Neuroleptic-induced supersensitivity psychosis. *Am J Psychiatry* 1978; 35:1409–1410.
5. Chouinard G, Jones BD. Neuroleptic-induced supersensitivity psychosis: clinical and pharmacologic characteristics. *Am J Psychiatry* 1980; 137:16–21.
6. Di Capite S, Upthegrove R, Mallikarjun P. The relapse rate and predictors of relapse in patients with first-episode psychosis following discontinuation of antipsychotic medication. *Early Interv Psychiatry* 2018; 12:893–899.
7. Zipursky RB, Menezes NM, Streiner DL. Risk of symptom recurrence with medication discontinuation in first-episode psychosis: a systematic review. *Schizophr Res* 2014; 152(2–3):408–414.
8. Harrow M, Jobe TH, Faull RN. Does treatment of schizophrenia with antipsychotic medications eliminate or reduce psychosis? A 20-year multifollow-up study. *Psychol Med* 2014; 44:3007–3016.
9. Harrow M, Jobe TH, Faull RN, Yang J. A 20-year multifollow up longitudinal study assessing whether antipsychotic medications contribute to work functioning in schizophrenia. *Psychiatry Res* 2017; 256:267–274.
10. Carpenter WT, McGlashan TH, Strauss JS. The treatment of acute schizophrenia without drugs: an investigation of some current assumptions. *Am J Psychiatry* 1977; 134:14–20.
11. Yin J, M Barr A, Ramos-Miguel A, M Procyshyn R. Antipsychotic induced dopamine supersensitivity psychosis: a comprehensive review. *Curr Neuropharmacol* 2017; 15:174–183.
12. Amada N, Akazawa H, Ohgi Y, et al. Brexpiprazole has a low risk of dopamine D2 receptor sensitization and inhibits rebound phenomena related to D2 and serotonin 5-HT2A receptors in rats. *Neuropsychopharmacol Rep* 2019; 39:279–288.
13. Hashimoto T, Baba S, Ikeda H, et al. Lack of dopamine supersensitivity in rats after chronic administration of blonanserin: Comparison with haloperidol. *Eur J Pharmacol* 2018; 830:26–32.
14. Charron A, El Hage C, Servonnet A, Samaha AN. 5-HT2 receptors modulate the expression of antipsychotic-induced dopamine supersensitivity. *Eur Neuropsychopharmacol* 2015; 25:2381–2393.
15. El Hage C, Bédard AM, Samaha AN. Antipsychotic treatment leading to dopamine supersensitivity persistently alters nucleus accumbens function. *Neuropharmacology* 2015; 99:715–725.
16. Tadokoro S, Okamura N, Sekine Y, et al. Chronic treatment with aripiprazole prevents development of dopamine supersensitivity and potentially supersensitivity psychosis. *Schizophr Bull* 2012; 38:1012–1020.
17. Aigbogun MS, Liu S, Kamat SA, et al. Relapse prevention: a cost-effectiveness analysis of brexpiprazole treatment in adult patients with schizophrenia in the USA. *Clinicoecon Outcomes Res* 2018; 10:443–456.
18. Varela FA, Der-Ghazarian T, Lee RJ, et al. Repeated aripiprazole treatment causes dopamine D2 receptor up-regulation and dopamine supersensitivity in young rats. *J Psychopharmacol* 2014; 28:376–386.
19. George SR, Watanabe M, Paolo TD, et al. The functional state of the dopamine receptor in the anterior pituitary is in the high affinity form. *Endocrinology* 1985; 117:690–697.
20. Seeman P, Weinschenker D, Quirion R, et al. Dopamine supersensitivity correlates with D2High states, implying many paths to psychosis. *Proc Natl Acad Sci USA* 2005; 102:3513–3518.
21. Samaha AN, Seeman P, Stewart J, et al. 'Breakthrough' dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time. *J Neurosci* 2007; 27:2979–2986.
22. Servonnet A, Minogianis EA, Bouchard C, et al. Neurotensin in the nucleus accumbens reverses dopamine supersensitivity evoked by antipsychotic treatment. *Neuropharmacology* 2017; 123:10–21.
23. Samaha AN, Reckless GE, Seeman P, et al. Less is more: antipsychotic drug effects are greater with transient rather than continuous delivery. *Biol Psychiatry* 2008; 64:145–152.
24. Servonnet A, Samaha AN. Antipsychotic-evoked dopamine supersensitivity. *Neuropharmacology* 2020; 163:107630.
25. Silvestri S, Seeman MV, Negrete JC, et al. Increased dopamine D2 receptor binding after long-term treatment with antipsychotics in humans: a clinical PET study. *Psychopharmacology* 2000; 152:174–180.
26. Mizrahi R, Agid O, Borlido C, et al. Effects of antipsychotics on D3 receptors: a clinical PET study in first episode antipsychotic naive patients with schizophrenia using [11C]-(-)-PHNO. *Schizophr Res* 2011; 131(1–3):63–68.
27. Howes OD, Kambeitz J, Kim E, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment: meta-analysis of imaging studies. *Arch Gen Psychiatry* 2012; 69:776–786.
28. Fallon P, Dursun S, Deakin B. Drug-induced supersensitivity psychosis revisited: characteristics of relapse in treatment-compliant patients. *Ther Adv Psychopharmacol* 2012; 2:13–22.

29. Fallon P, Dursun SM. A naturalistic controlled study of relapsing schizophrenic patients with tardive dyskinesia and supersensitivity psychosis. *J Psychopharmacol* 2011; 25:755–762.
30. Emsley R, Nuamah I, Gopal S, *et al.* Relapse after antipsychotic discontinuation in schizophrenia as a withdrawal phenomenon vs illness recurrence: a post hoc analysis of a randomized placebo-controlled study. *J Clin Psychiatry* 2018; 79:17m11874.
31. Shin SH, Kim S, Kim E. Antipsychotic discontinuation in first episode psychosis: [18F] DOPA and [11C] raclopride PET study. *Schizophrenia International Research Society (SIRS) conference 2018; 2018-04-07; Florence, Italy.*
- A recent study, presented at SIRS (Italy), investigated whether dopaminergic function changes after the discontinuation of antipsychotic medication. The results showed no difference between relapsed and nonrelapsed patients in dopamine D₂ availability. Interestingly, relapsed patients did show an increase in dopamine synthesis, compared to nonrelapsed patients, suggesting that relapsed patients could be different in the underlying pathophysiology, such as a presynaptic abnormality.
32. Kanahara N, Yoshimura K, Nakamura M, *et al.* Metabolism of risperidone by CYP2D6 and the presence of drug-induced dopamine supersensitivity psychosis in patients with schizophrenia. *Int Clin Psychopharmacol* 2019; 34:124–130.
33. Seeman P. All roads to schizophrenia lead to dopamine supersensitivity and elevated dopamine D₂ receptors. *CNS Neurosci Ther* 2011; 17:118–132.
34. Kubota M, Nagashima T, Takano H, *et al.* Affinity states of striatal dopamine D₂ receptors in antipsychotic-free patients with schizophrenia. *Int J Neuropsychopharmacol* 2017; 20:928–935.
35. Chouinard G, Samaha AN, Chouinard VA, *et al.* Antipsychotic-induced dopamine supersensitivity psychosis: pharmacology, criteria, and therapy. *Psychother Psychosom* 2017; 86:189–219.
36. Takeuchi H, Siu C, Remington G, *et al.* Does relapse contribute to treatment resistance? Antipsychotic response in first-vs. second-episode schizophrenia. *Neuropsychopharmacology* 2019; 44:1036.
- A recent study linking relapse in patients with a first psychotic episode with increasing treatment resistance; results showed that patients who discontinued antipsychotic medication after being in remission and subsequently relapsed may continue with the same dose, although treatment response may be attenuated or delayed.
37. Wunderink L, Nieboer RM, Wiersma D, *et al.* Recovery in remitted first-episode psychosis at 7 years of follow-up of an early dose reduction/discontinuation or maintenance treatment strategy: long-term follow-up of a 2-year randomized clinical trial. *JAMA Psychiatry* 2013; 70:913–920.