# Role OF 5-HT2C receptors in dyskinesia

Loonen, Anton J. M.; Ivanova, Svetlana A.

*Published in:*
International Journal of Pharmacy and Pharmaceutical Sciences



*Publication date:*
2016

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 8, Issue 1, 2016

Review Article

# ROLE OF 5-HT2C RECEPTORS IN DYSKINESIA

**ANTON J. M. LOONEN[a,b*], SVETLANA A. IVANOVA[c,d]**

[a]Department of Pharmacy, University of Groningen, Antonius Deusinglaan 1, 9713AV Groningen, The Netherlands, [b]Mental Health Institute GGZ Westelijk Noord-Brabant, Halsteren, The Netherlands, [c]Mental Health Research Institute, Tomsk, Siberia, Russian Federation, [d]National Research Tomsk Polytechnic University, Tomsk, Siberia, Russian Federation
Email: a.j.m.loonen@rug.nl

*Received: 27 Aug 2015 Revised and Accepted: 18 Nov 2015*

**ABSTRACT**

By integrating knowledge gained by pharmacogenetic, neuroanatomical and pharmacological studies, a model can be constructed how serotonin (5-HT) affects the vulnerability to induce tardive dyskinesia. From neuroanatomical studies, it can be concluded that 5-HT inhibits the release of dopamine (DA) within the dorsal striatum by affecting 5-HT2C receptors and also within the ventral striatum and prefrontal cortex by affecting 5-HT2A receptors. However, considering the low affinity of DA for its receptors, it is unlikely that the so released DA is able to displace atypical antipsychotics from DA D2 and D3 receptors. 5-HT2C receptors and, to a lesser extent, 5-HT2A receptors, have constitutive activity and therefore, atypical antipsychotics can have inverse agonistic effects. It is hypothesized that decreasing the activity of 5-HT2 receptor carrying medium spiny neurons (MSNs) within the dorsal striatum represents the mechanism showing how atypical antipsychotics have limited ability to cause tardive dyskinesia.

**Keywords:** Tardive dyskinesia, Extrapyramidal system, Medium spiny neurons, 5-HT2C receptors, Inverse agonism.



## INTRODUCTION

Dyskinesia is a movement disorder characterized by involuntary, repetitive and irregular motions that affect the mouth and face and/or the limbs and trunk [1, 2]. Dyskinesia can occur spontaneously, particularly in elderly patients [3, 4], and in persons with schizophrenia [5-7], in Huntington's disease and in a variety of other neurological disorders [8], and can be drug-induced [9]. The usage of antipsychotic drugs and levodopa, in particular has been associated with dyskinesia. Tardive dyskinesia (TD) is a well-known complication of long-term treatment with dopamine (DA) blocking agents, predominantly antipsychotic drugs [10]. Levodopa-induced dyskinesia (LID) is a common consequence of the long-term treatment of Parkinson's disease with levodopa [11-14].

Both LID and TD are believed to be caused by a dysregulation of the DAergic neurotransmitter system. A well-accepted model of LID states that the mechanism underlying these movements is related to pulsatile stimulation of postsynaptic DA receptors [14]. A classical model of the pathogenesis of TD explains this movement disorder to be a super sensitivity response to chronic DA blockade [15]. However, the 5-HTergic system is also believed to be involved [15-18].

Seven types of serotonin (5-hydroxytryptamine; 5-HT) receptors have been found, all but one (5-HT3) being g-protein coupled [19-21]. Most of these are divided into several subtypes. For their role in dyskinesia, 5-HT1A, 5-HT2A and 5-HT2C receptors have been most extensively studied [17, 22]. Stimulation of 5-HT1A receptors result in increased influx of $K^+$ions and hyperpolarization of the membrane, and so to the inhibition of neurotransmission while 5-HT2A and 5-HT2C receptors have opposite activity [19-24].

Pharmacogenetic studies describe an association between polymorphisms of the genes coding for the 5-HT2A (*HTR2A*) and 5-HT2C (*HTR2C*) receptor protein and the prevalence of tardive dyskinesia. The results appear to be conflicting [25], however. The 23Ser allele of the Cys23Ser variants of *HTR2C* (rs6318) was associated with an increased risk of TD and Parkinsonism [26-30]. The *HTR2C* is found on the long arm of the X-chromosome, Xq24 [31]. Males, therefore, are hemizygotes, so always homozygous. Al Hadithy *et al.* demonstrated there was a significant association between carriers of the 23Ser allele of *HTR2C* and Parkinsonian bradykinesia in males, but not in females [26]. Wilffert *et al.* did not find a correlation between TD and 23Ser male carriers when they were analyzed separately [30]. Orofacial and limb-truncal TD scores, however, were statistically significantly higher in male patients carrying combinations of the 9Ser variant of the DA D3 (*DRD3*) gene and 23Ser allele of *HTR2C* [30]. This may correspond to the findings of Segman *et al.*, who found no association with 23Ser male carriers, but the highest orofacial dyskinesia scores were found in combined carriers of 9Gly *DRD3* and 23Ser *HTR2C* (not specified for males and females) [29]. Gunes *et al.*, who studied only male subjects with several types of EPS (Parkinsonism, dystonia, and/or dyskinesia), observed a strong association with 23Ser *HTR2C* carriers [28]. It should be emphasized that the drug treatments probably differed between studies. Gunes *et al.* excluded all patients who were using atypical drugs,[28] while the other authors included patients who were on atypical antipsychotics [26,27,30]. Unfortunately, Segman *et al.* did not specify the antipsychotics used by their patient population, but they studied Jewish patients recruited from several centers in Israel [29, 32].

Atypical antipsychotics are assumed to cause less Parkinsonism and TD by blocking 5-HT2A and/or 5-HT2C (5-HT2A/2C) receptors [33-36], therefore, the differences between the results of these studies may at least be partly explained by the concurrent use of 5-HT2A/2C blocking agents by at least some of the patients, which apparently decrease the differences between carriers and non-carriers. In future studies, users of 5-HT2A/2C blocking agents should be excluded from analysis.

In this article, we will try to explain the association between being a carrier of this 23Ser *HTR2C,* and the likelihood of developing TD by describing the distribution and physiological role of this receptor.

### Anatomical considerations

5-HT is, together with DA, norepinephrine (NE) and histamine (H), one of the lesser abundant neurotransmitters of the central nervous system (CNS), which are used by about 2% of the CNS nerve cells [19]. Cell bodies of 5-HTergic neurons are primarily localized in a group of five nuclei near the midline ('raphe' from Greek ῥαφή) of the brainstem (fig. 1). Apart from these proper raphe nuclei, three other nuclei have been described [37]. These nuclei are usually divided into upper and lower raphe nuclei. From there, at least six bundles of fibers can be distinguished, which run up and down to most parts of the CNS, including a bundle running to preganglionic sympathetic neurons of the thoracic intermediolateral column

within the spinal cord and one up through the medial forebrain bundle to the striatum and cerebral cortex [19, 37]. Within the brainstem, 5-HTergic nuclei are connected to the DAergic substantia nigra, pars compacta (SNc) and ventral tegmental nucleus (VTA), to adrenergic (NE using) locus coeruleus and nucleus tractus solitarius and to other 5-HTergic raphe nuclei [19, 37].

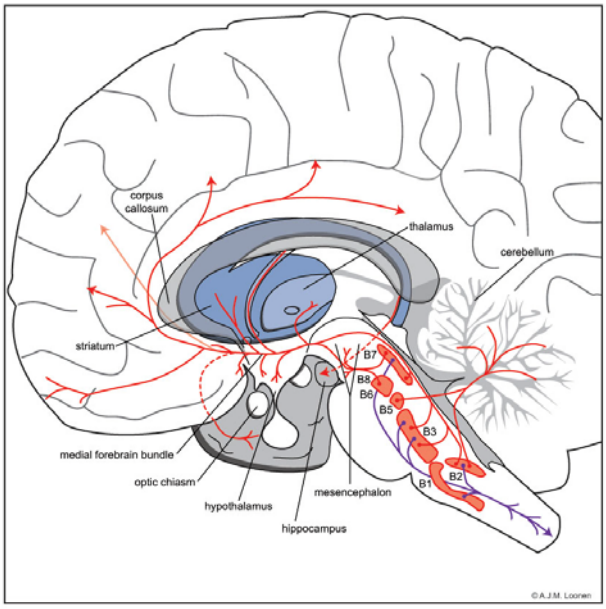


**Fig. 1: Serotonergic system [19]**

B1: nucleus raphes pallidus, B2: nucleus raphes obscurus, B3 nucleus raphes magnus, B5 nucleus raphes pontis, B7 nucleus raphes dorsalis, B6+B8: nucleus centralis superior, B4 and B9 innominate cell groups.

In order to understand how 5-HT2 receptors modify Parkinsonism and TD, the exact localization of 5-HT2A and 5-HT2C receptors within several areas of the brain should be considered. This localization is not entirely clear within the cerebral cortex [36, 38]. 5-HT2A receptors are abundantly present in the telencephalon (olfactory system, cerebral cortex, basal forebrain, neostriatum, and hippocampus), and occur in the diencephalon and brainstem [36]. 5-HT2C receptors are more abundant and more widely expressed than 5-HT2A receptors, but the two types of receptors often co-exist [36].

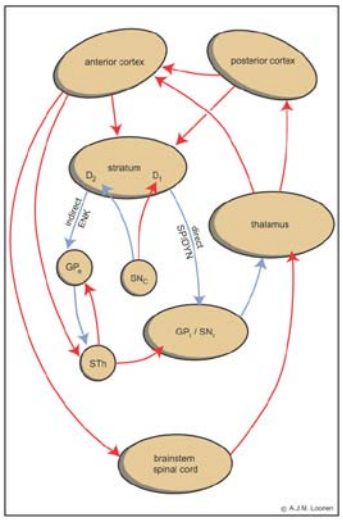


**Fig. 2: Schematic representation of extrapyramidal system with direct and indirect pathways [19]**

D1 = dopamine D1 receptor carrying MSNs, D2 = dopamine D2 receptor carrying MSNs, DYN = dynorphin, ENK = enkephalin, GPe = globus pallidus external part, GPi = globus pallidus internal part, SNc = substantia nigra pars compacta, SNr = substantia nigra pars reticulata, SP = substance P, STh = subthalamic nucleus; in red = excitatory pathways, in blue = inhibitory pathways.

Within the cerebral cortex, 5-HT2A receptors are localized on pyramidal cells, on Gamma Amino Butyric Acid (GABA)ergic interneurons, and pre-synaptically on axons of (probably) monoaminergic cells (fig. 3). However, although results are conflicting, 5-HT2C receptors are probably not present on fast-spiking (i.e. GABAergic) interneurons of the cerebral cortex [36, 38, 39]. Within the basal ganglia, 5-HT2A and 5-HT2C receptors are co-localized within medium-sized spiny projection neurons (MSNs) of both direct and indirect pathways of the extrapyramidal circuit (fig. 2 and 4) [36]. Moreover, both 5-HT2A and 5-HT2C receptors are present on cholinergic, glutamatergic, and DAergic axon terminals [38]. The simultaneous role in GABAergic interneurons is less clear. 5-HT acts on 5-HT2C receptors when stimulating striatal fast-spiking interneurons, which are the most numerous class of GABAergic interneurons there [40]. To the best of our knowledge, a physiological role has never been established for 5-HT2A receptors. Within the upper brainstem, 5-HT2C receptors are restricted to GABAergic neurons, at least within pars reticulata and pars compacta (SNc) of the substantia nigra (fig. 5). Only few 5-HT2C receptor positive cells were observed within the VTA [41]. However, 5-HT2A receptors were more often present within neurons in the VTA than those in the SNc [42]. Within the VTA, 5-HT2A receptors are unevenly distributed and more prevalent in rostral and mid parts [43]. They are co-localized with DAergic neurons throughout the VTA, but they also co-localized with non-DAergic cells [43]. These differences in the distributions of 5-HT2A and 5-HT2C receptors may explain the various effects of 5-HT agonists and antagonists in different parts of the midbrain. Within the VTA, they predominantly act on 5-HT2A receptors with a direct effect on DAergic neurons, while within the SNc, they predominantly act on 5-HT2C receptors of GABAergic interneurons.

It can be concluded that 5-HT inhibits the activity of DA terminals within the dorsal striatum, mainly by affecting 5-HT2C receptors. It inhibits DA activity within the ventral striatum and frontal cortex mainly by affecting 5-HT2A receptors.

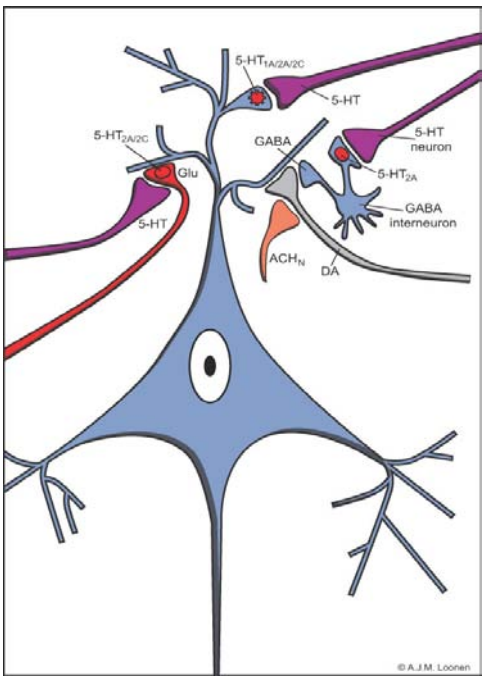


**Fig. 3: Distribution of 5-HT2A and 5-HT2C receptors within the prefrontal cortex [19]**

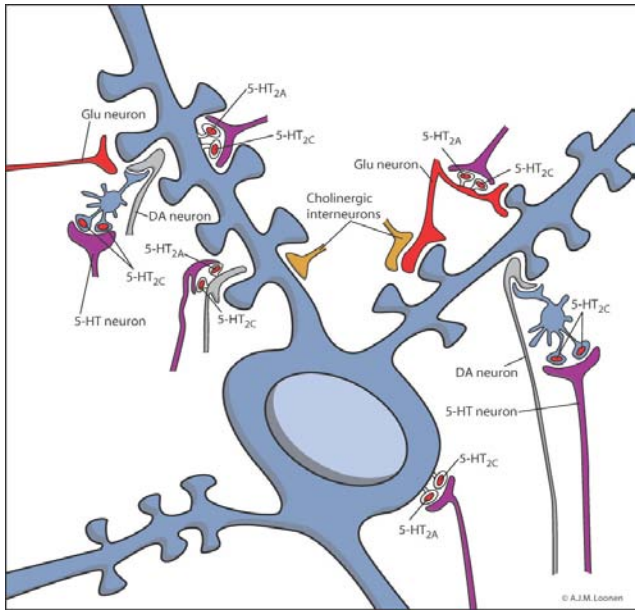


**Fig. 4: Distribution of 5-HT2A and 5-HT2C receptors within the striatum [original]**

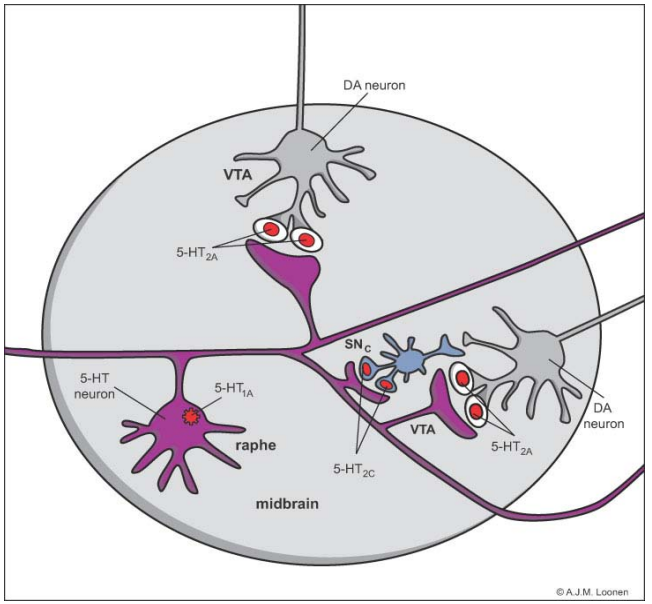


**Fig. 5: Distribution of 5-HT2A and 5-HT2C receptors within the midbrain [original]**

**Table 1: Receptor-binding affinities (expressed as Ki values) of several atypical antipsychotic agents in comparison to haloperidol**

| | Clozapine | Olanzapine | Quetiapine | Ziprasidone | Sertindole | Aripiprazol | Asenapine | Risperidon | Paliperidon | Pipamperon | Ritanserin | Haloperidol |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| D1 | 85 | 31 | 455 | 9.5 | 12 | 265 | 1.4 | 75 | 670 | - | - | 25 |
| D2 | 125 | 11 | 160 | 4.8 | 0.45 | 0.34 | 1.4 | 3 | 4.0 | 124 | 70 | 1 |
| D3 | 473 | 49 | 340 | 7.2 | 12 | 0.8 | 0.42 | 10 | 7.5 | - | - | 2 |
| D4 | 9 | 27 | 1600 | 32 | 11 | 44 | 1.1 | 7 | 30 | - | - | 5 |
| D5 | 235 | 90 | 1738 | 152 | - | 1675 | - | 16 | 29 | - | - | 147 |
| 5-HT$_{2A}$ | 12 | 4 | 220 | 0.4 | 0.2 | 3.4 | 0.07 | 0.6 | 0.25 | 7 | 1.0 | 78 |
| 5-HT$_{2C}$ | 8 | 11 | 615 | 1.3 | 0.51 | 15 | 0.034 | 26 | 71 | 54 | 9.3 | 3085 |
| $\alpha_1$ | 7 | 19 | 7 | 10 | 1.4 | 57 | 1.2 | 2 | 4.0 | 62 | 97 | 46 |
| $H_1$ | 6 | 7 | 11 | 47 | 440 | 61 | 1.0 | 155 | 10 | >> | 35 | 3630 |
| $M_1$ | 1,9 | 1.9 | 120 | >> | 260 | >> | >> | >> | 3570 | 2.500 | - | 1475 |

Aripiprazole [Abilify package insert]; asenapine [50]; olanzapine [Zyprexa package insert]; paliperidone [51]; pipamperone [52, 53]; ritanserin [54]; sertindole [55]; ziprasidone [Gideon package insert]; D5: [22, 56, 57].

**How antagonizing 5-ht2 receptor does limits Parkinsonism and dyskinesia**

An initial model to explain how atypical antipsychotics cause less extrapyramidal side effects than classical drugs was related to the observation that antagonists of 5-HT2 receptors block the inhibition of release of DA by 5-HT from striatal slices *in vitro* [44]. It was suggested that 5-HT had this effect by stimulating 5-HT2 receptors on DAergic terminals. Later, it was shown that numerous atypical antipsychotics stimulate the release of DA more potently in the medial prefrontal cortex and mesocorticolimbic innervated areas than in the striatum [45]. This is not only attributed to direct effects on DAergic terminals, but also influencing their origins within the midbrain. However, 5-HT2C receptors mediate an inhibitory effect on the release of DA within the dorsal and ventral striatum [45, 46]. As has been stated above, both 5-HT2A and 5-HT2C receptors have an excitatory effect [19-21], so blocking these receptors with atypical antipsychotics would result in inhibition of the DAergic cell bodies/terminals and therefore, result in inhibition of DA release. This apparent contradiction can be explained by their localization on GABAergic inhibitory interneurons [47].

Stimulation of these interneurons results in inhibition of the activity of DAergic cells and nerve terminals; blocking these 5-HT2 receptors would result in increased release of DA [19]. Based on this theory, it was believed that atypical antipsychotics induce the release of DA to such an extent that some of the DA D2 receptor blockades by the antipsychotic drug was reversed [48]. However, an important pharmacological reason causes doubt concerning this mechanism. As can be seen in table 1, apart from clozapine, quetiapine, and pipamperone, most atypical antipsychotics are potent DA D2 receptor antagonists. DA itself has an affinity in the micromolar range [49]. It is difficult to understand how the even massive release of DA would be able to displace most atypical antipsychotics to a sufficient degree from their DA D2 receptor. In fact, this mechanism would overload the putamen with DA, leading to an increase in oxidative stress. This may result in an increase of TD by causing damage to medium sized GABAergic projection neurons (MSNs) [10].

Apart from promoting DA release from striatal DAergic fibers, 5-HT2 receptors may modulate the activity of striatal GABAergic projection neurons (MSNs) directly (fig. 4). These receptors are present on MSNs of both direct and indirect pathways. A special characteristic of these receptors can explain why 5-HT2 antagonists diminish Parkinsonism and decrease the likelihood of developing dyskinesia: these receptors spontaneously signal for cellular effector mechanisms in the absence of ligands [38, 58], and 5-HT2C receptors may have higher constitutive activity than 5-HT2A. In this situation, a ligand binding to the receptor may also act as an inverse agonist; i.e., changing the activity of the receptor in the opposite direction instead of increasing or blocking it. This occurred when this receptor was bound by atypical antipsychotics [22, 38]. This may also explain the findings from genetic studies. In these cases, the genetic variant (of 5-HT2A or 5-HT2C receptors) with increased constitutive activity would have greater benefit and the variant with decreased or absent constitutive activity would have less benefit due to the complete blockade of these receptors by atypical antipsychotic drugs. In the absence of receptor blockers (usage of classical antipsychotics), carriers of a variant with no constitutive activity would have a significant advantage. As is shown in table 1, most atypical antipsychotics are both 5-HT2A and 5-HT2C antagonists. Inverse agonism is somewhat more likely with 5-HT2C than 5-HT2A receptors [38]. Moreover, inverse agonism at 5-HT2C receptors may also explain the prevention of TD by having a direct influence on MSNs and/or an indirect effect on corticostriatal projections. Inverse agonistic effects (less activation) on MSNs of the indirect pathway could explain the occurrence of less Parkinsonism as well as protection against excitatory toxicity [10].

**CONCLUSION**

Considering the distribution of these receptors and the low affinity of DA to receptors of the DA D2 receptor family, it seems unlikely that atypical antipsychotics have a low potential to cause Parkinsonism by increasing DA release within the striatum. Only clozapine, quetiapine and pipamperone have such low affinity to the D2 receptors that DA could successfully compete with them for binding to this receptor.

An exception may be binding to the Ser9Gly *DRD3* variant (rs6280) of the DA D3 receptor [59]. The homogenous Gly variant has been associated with four-fold greater DA binding affinity *in vitro* [60] and the DA D3 receptor is characterized by an extraordinary large binding affinity for DA [61]. It should be emphasized, however, that DA D3 receptors are largely confined to the ventral striatum [61], while the site of action of TD inducing mechanisms should be the putamen [10]. So, even in this case, promoting DA release is an unlikely mechanism to overcome antipsychotic drug-induced Parkinsonism. Furthermore, even when DA would have sufficient affinity to compete with antipsychotics for binding to the homogenous Ser9Gly variant of the DA D3 receptor, it is difficult to understand how this activation could overcome the remaining blockade of DA D2 and D4 receptors within the dorsal striatum.

Whether the affinity of atypical antipsychotics to DA D1 and D5 receptors is sufficiently low to have these drugs displaced by extra released DA (table 1), is not certain, but definitely more likely: this could be related to the cognitive effects of atypical antipsychotics [22]. Moreover, the release of DA within the prefrontal cortex has a higher magnitude than that within the dorsal striatum possibly by the involvement of 5-HT2A receptors [45]. The release of DA within the prefrontal cortex and striatum may be relevant in case of antidepressant drugs because these agents have a very low affinity to DA receptors [62].

So, when the promoting of DA release is not the best explanation for the reduced capability of 5-HT2 receptor antagonists to induce Parkinsonism and TD in comparison to classical antipsychotics, an alternative explanation comes into view. We want to hypothesize that this is caused by blocking the constitutive excitatory activity of 5-HT2 receptors on striatal MSNs (fig. 4). This would decrease the activation of both direct and indirect extrapyramidal pathways, thereby reducing the risk of Parkinsonism, especially when the direct pathway is still activated by stimulation of DA D1 carrying MSNs. At the same time it would lower the vulnerability of these medium spiny neurons (MSNs) to neurotoxicity resulting from oxidative stress, therewith preventing TD [10].

**ACKNOWLEDGEMENT**

This work was in part supported by the Russian Science Foundation [Grant #14-35-00023].

**CONFLICT OF INTERESTS**

The authors declare that there is no conflict of interest regarding the publication of this paper.

**REFERENCES**

1. Loonen AJ, van Praag HM. Measuring movement disorders in antipsychotic drug trials: the need to define a new standard. J Clin Psychopharmacol 2007;27:423-30.
2. Aquino CC, Lang AE. Tardive dyskinesia syndromes: current concepts. Parkinsonism Related Disorders 2014;20 Suppl 1:S113-7.
3. Clark GT, Ram S. Four oral motor disorders: bruxism, dystonia, dyskinesia and drug-induced dystonic extrapyramidal reactions. Dent Clin North Am 2007;51:225-43.
4. Woerner MG, Kane JM, Lieberman JA, Alvir J, Bergmann KJ, Borenstein M, *et al.* The prevalence of tardive dyskinesia. J Clin Psychopharmacol 1991;11:34-42.
5. Kane JM, Smith JM. Tardive dyskinesia: prevalence and risk factors, 1959 to 1979. Arch Gen Psychiatry 1982;39:473-81.
6. Pappa S, Dazzan P. Spontaneous movement disorders in antipsychotic-naive patients with first-episode psychoses: a systematic review. Psychol Med 2009;39:1065-76.
7. Tenback DE, van Harten PN. Epidemiology and risk factors for (tardive) dyskinesia. Int Rev Neurobiol 2011;98:211-30.
8. Wild EJ, Tabrizi SJ. The differential diagnosis of chorea. Pract Neurol 2007;7:360-73.
9. Zesiewicz TA, Sullivan KL. Drug-induced hyperkinetic movement disorders by nonneuroleptic agents. Handb Clin Neurol 2011;100:347-63.

10. Loonen AJ, Ivanova SA. New insights into the mechanism of drug-induced dyskinesia. CNS Spectrums 2013;18:15-20.
11. Bargiotas P, Konitsiotis S. Levodopa-induced dyskinesias in Parkinson's disease: emerging treatments. Neuropsychiatr Dis Treat 2013;9:1605-17.
12. Del Sorbo F, Albanese A. Levodopa-induced dyskinesias and their management. J Neurol 2008;255 Suppl 4:32-41.
13. Manson A, Stirpe P, Schrag A. Levodopa-induced-dyskinesias clinical features, incidence, risk factors, management and impact on quality of life. J Parkinson's Dis 2012;2:189-98.
14. Thanvi BR, Lo TC. Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. Postgrad Med J 2004;80:452-8.
15. Glazer WM. Extrapyramidal side effects, tardive dyskinesia, and the concept of atypicality. J Clin Psychiatry 2000;61 Suppl 3:16-21.
16. Cheshire PA, Williams DR. Serotonergic involvement in levodopa-induced dyskinesias in Parkinson's disease. J Clin Neurosci 2012;19:343-8.
17. Huot P, Johnston TH, Koprich JB, Fox SH, Brotchie JM. The pharmacology of L-DOPA-induced dyskinesia in Parkinson's disease. Pharmacol Rev 2013;65:171-222.
18. Sandyk R, Fisher H. Serotonin in involuntary movement disorders. Int J Neurosci 1988;42:185-208.
19. Loonen AJ. Het beweeglijke brein. De neurowetenschappelijke achtergronden van de psychische functies. Haarlem, NL: Mension Publisher; 2013.
20. Hoyer D, Hannon JP, Martin GR. Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol Biochem Behav 2002;71:533-54.
21. Hannon J, Hoyer D. Molecular biology of 5-HT receptors. Behav Brain Res 2008;195:198-213.
22. Meltzer HY. Serotonergic mechanisms as targets for existing and novel antipsychotics. In: G Gross, MA Geyer. (eds.) Current antipsychotics. Handb Exp Pharmacol 2012;212:87-124.
23. Stiedl O, Pappa E, Konradsson-Geuken Å, Ögren SO. The role of the serotonin receptor subtypes 5-HT1A and 5-HT7 and its interaction in emotional learning and memory. Front Pharmacol 2015;6:162.
24. Howell LL, Cunningham KA. Serotonin 5-HT2 receptor interactions with dopamine function: implications for therapeutics in cocaine use disorder. Pharmacol Rev 2015;67:176-97.
25. Arranz MJ, Rivera M, Munro JC. Pharmacogenetics of response to antipsychotics in patients with schizophrenia. CNS Drugs 2011;25:933-69.
26. Al Hadithy AF, Wilffert B, Stewart RE, Looman NM, Bruggeman R, Brouwers JR, *et al.* Pharmacogenetics of parkinsonism, rigidity, rest tremor, and bradykinesia in African-Caribbean inpatients: differences in association with dopamine and serotonin receptors. Am J Med Genet Part B 2008;5;147B:890-7.
27. Al Hadithy AF, Wilffert B, Bruggeman R, Stewart RE, Brouwers JR, Matroos GE, *et al.* Lack of association between antipsychotic-induced Parkinsonism or its subsymptoms and rs4606 SNP of RGS2 gene in African-Caribbeans and the possible role of the medication: the Curacao extrapyramidal syndromes study X. Hum Psychopharmacol 2009;24:123-8.
28. Gunes A, Dahl ML, Spina E, Scordo MG. Further evidence for the association between 5-HT2C receptor gene polymorphisms and extrapyramidal side effects in male schizophrenic patients. Eur J Clin Pharmacol 2008;64:477-82.
29. Segman RH, Heresco-Levy U, Finkel B, Inbar R, Neeman T, Schlafman M, *et al.* Association between the serotonin 2C receptor gene and tardive dyskinesia in chronic schizophrenia: additive contribution of 5-HT2Cser and DRD3gly alleles to susceptibility. Psychopharmacology (Berl) 2000;152:408-13.
30. Wilffert B, Al Hadithy AF, Sing VJ, Matroos G, Hoek HW, van Os J, *et al.* The role of dopamine D3, 5-HT2A and 5-HT2C receptor variants as pharmacogenetic determinants in tardive dyskinesia in African-Caribbean patients under chronic antipsychotic treatment: Curacao extrapyramidal syndromes study IX. J Psychopharmacol 2009;23:652-9.
31. Milatovich A, Hsieh CL, Bonaminio G, Tecott L, Julius D, Francke U. Serotonin receptor 1c gene assigned to X chromosome in human (band q24) and mouse (bands D-F4). Hum Mol Genet 1992;1:681-4.
32. Segman R, Neeman T, Heresco-Levy U, Finkel B, Karagichev L, Schlafman M, *et al.* Genotypic association between the dopamine D3 receptor and tardive dyskinesia in chronic schizophrenia. Mol Psychiatry 1999;4:247-53.
33. Duinkerke SJ, Botter PA, Jansen AA, van Dongen PA, van Haaften AJ, Boom AJ, *et al.* Ritanserin, a selective 5-HT2/1C antagonist, and negative symptoms in schizophrenia. A placebo-controlled double-blind trial. Br J Psychiatry 1993;163:451-5.
34. Grant S, Fitton A. Risperidone. A review of its pharmacology and therapeutic potential in the treatment of schizophrenia. Drugs 1994;48:253-73.
35. Owens DG. Extrapyramidal side effects and tolerability of risperidone: a review. J Clin Psychiatry 1994;55 Suppl:29-35.
36. Leysen JE. 5-HT2 receptors. Curr Drug Targets CNS Neurol Disord 2004;3:11-26.
37. Nieuwenhuys R. Chemoarchitecture of the brain. Berlin: Springer-Verlag; 1985.
38. Aloyo VJ, Berg KA, Spampinato U, Clarke WP, Harvey JA. Current status of inverse agonism at serotonin2A (5-HT2A) and 5-HT2C receptors. Pharmacol Ther 2009;121:160-73.
39. Celada P, Puig MV, Artigas F. Serotonin modulation of cortical neurons and networks. Front Integr Neurosci 2013;7:25.
40. Blomeley CP, Bracci E. Serotonin excites fast-spiking interneurons in the striatum. Eur J Neurosci 2009;29:1604-14.
41. Eberle-Wang K, Mikeladze Z, Uryu K, Chesselet MF. The pattern of expression of the serotonin2C receptor messenger RNA in the basal ganglia of adult rats. J Comp Neurol 1997;384:233-47.
42. Ikemoto K, Nishimura A, Okado N, Mikuni M, Nishi K, Nagatsu I. Human midbrain dopamine neurons express serotonin 2A receptor: an immunohistochemical demonstration. Brain Res 2000;853:377-80.
43. Nocjar C, Roth BL, Pehek EA. Localization of 5-HT(2A) receptors on dopamine cells in subnuclei of the midbrain A10 cell group. Neuroscience 2002;111:163-76.
44. Muramatsu M, Tamaki-Ohashi J, Usuki C, Araki H, Chaki S, Aihara H. 5-HT2 antagonists and minaprine block the 5-HT-induced inhibition of dopamine release from rat brain striatal slices. Eur J Pharmacol 1988;153:89-95.
45. Di Matteo V, Di Giovanni G, Pierucci M, Esposito E. Serotonin control of central dopaminergic function: focus on *in vivo* microdialysis studies. Prog Brain Res 2008;172:7-44.
46. Di Matteo V, Pierucci M, Esposito E, Crescimanno G, Benigno A, Di Giovanni G. Serotonin modulation of the basal ganglia circuitry: therapeutic implication for Parkinson's disease and other motor disorders. Prog Brain Res 2008;172:423-63.
47. Fink KB, Göthert M. 5-HT receptor regulation of neurotransmitter release. Pharmacol Rev 2007;59:360-417.
48. Casey DE. Pathophysiology of antipsychotic drug-induced movement disorders. J Clin Psychiatry 2004;65 Suppl9:25-8.
49. Seeman P. Brain dopamine receptors. Pharmacol Rev 1980;32:229-313.
50. Chwieduk CM, Scott LJ. Asenapine: a review of its use in the management of mania in adults with bipolar I disorder. CNS Drugs 2011;25:251-67.
51. Schotte A, Janssen PF, Gommeren W, Luyten WH, Van Gompel P, Lesage AS, *et al.* Risperidone compared with new and reference antipsychotic drugs: *in vitro* and *in vivo* receptor binding. Psychopharmacology (Berl) 1996;124:57-73.
52. Leysen JE. Receptors for antipsychotic drugs. In: GD Burrows, JS Werry. (eds). Adv Hum Psychopharmacology. Greenwich, CT: JAI Press Inc; 1982.
53. Oekelen DV, Jurzak M, Van de Wiel D, Van Hecke G, Luyten WH, Leysen JE. Different regulation of rat 5-HT(2A) and rat 5-HT(2C) receptors in NIH 3T3 cells upon exposure to 5-HT and pipamperone. Eur J Pharmacol 2001;425:21-32.
54. Leysen JE, Gommeren W, Van Gompel P, Wynants J, Janssen PF, Laduron PM. Receptor-binding properties *in vitro* and *in vivo* of ritanserin: A very potent and long-acting serotonin-S2 antagonist. Mol Pharmacol 1985;27:600-11.
55. Arnt J, Skarsfeldt T. Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence. Neuropsychopharmacology 1998;18:63-101.

56. Bymaster FP, Calligaro DO, Falcone JF, Marsh RD, Moore NA, Tye NC, *et al.* Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 1996;14:87-96.
57. Richtand NM, Welge JA, Logue AD, Keck PE Jr, Strakowski SM, McNamara RK. The role of serotonin and dopamine receptor binding in antipsychotic efficacy. Prog Brain Res 2008;172:155-75.
58. Sullivan LC, Clarke WP, Berg KA. Atypical antipsychotics and inverse agonism at 5-HT2 receptors. Curr Pharm Des 2015;21:3732-8.
59. Lencz T, Malhotra AK. Pharmacogenetics of antipsychotic-induced side effects. Dialogues Clin Neurosci 2009;11:405-15.
60. Lundstrom K, Turpin MP. Proposed schizophrenia-related gene polymorphism: expression of the Ser9Gly mutant human dopamine D3 receptor with the semliki forest virus system. Biochem Biophys Res Commun 1996;225:1068-72.
61. Schwartz JC, Levesque D, Martres MP, Sokoloff P. Dopamine D3 receptor: basic and clinical aspects. Clin Neuropharmacol 1993;16:295-314.
62. Richelson E. Pharmacology of antidepressants. Mayo Clin Proc 2001;76:511-27.