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RESEARCH ARTICLE

No evidence so far of a major role of *AKT1* and *GSK3B* in the pathogenesis of antipsychotic-induced tardive dyskinesia

Anastasia Levchenko^{1*} | Natalya Vyalova^{2*} | Ivan V. Pozhidaev² | Anastasiia S. Boiko² | Diana Z. Osmanova² | Olga Yu. Fedorenko^{2,3} | Arkadiy V. Semke² | Nikolay A. Bokhan^{2,4} | Bob Wilffert^{5,6} | Anton J.M. Loonen^{5,7} | Svetlana A. Ivanova^{2,3}

¹Institute of Translational Biomedicine, Saint Petersburg State University, Saint Petersburg, Russia

²Tomsk National Research Medical Center of the Russian Academy of Sciences, Mental Health Research Institute, Tomsk, Russia

³Division for Control and Diagnostics, School of Non-Destructive Testing & Security, National Research Tomsk Polytechnic University, Tomsk, Russia

⁴Department of Psychotherapy and Psychological Counseling, National Research Tomsk State University, Tomsk, Russia

⁵Unit of Pharmacotherapy, Epidemiology and Economics, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands

⁶Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

⁷GGZ Westelijk Noord-Brabant, Bergen op Zoom, The Netherlands

Correspondence

Anastasia Levchenko, Institute of Translational Biomedicine, Saint Petersburg State University, 7/9, Universitetskaya Embankment, Saint Petersburg 199034, Russia.
Email: a.levchenko@spbu.ru

Natalya Vyalova, Mental Health Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences, 4, Aleutskaya Street, Tomsk 634014, Russia.
Email: natarakitina@yandex.ru

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Abstract

Objective: *AKT1* and *GSK3B* take part in one of the intracellular cascades activated by the D2 dopamine receptor (DRD2). This receptor is antagonized by antipsychotics and plays a role in the pathogenesis of antipsychotic-induced tardive dyskinesia (TD). The present study investigated association of several polymorphisms in the two candidate genes, *AKT1* and *GSK3B*, with TD in antipsychotic-treated patients with schizophrenia.

Methods: DNA samples from 449 patients from several Siberian regions (Russia) were genotyped, and the results were analyzed using chi-squared tests and analyses of variance.

Results: Antipsychotic-induced TD was not associated with either of the tested functional polymorphisms (rs334558, rs1130214, and rs3730358).

Conclusions: Despite regulation of *AKT1* and *GSK3B* by DRD2, we found no evidence that these two kinases play a major role in the pathogenesis of antipsychotic-induced TD. These results agree with previously published data and necessitate further exploration of other pathogenic mechanisms, such as neurotoxicity due to excessive dopamine metabolism.

KEYWORDS

AKT1, antipsychotics, *GSK3B*, pharmacogenetics, schizophrenia, tardive dyskinesia

1 | INTRODUCTION

Iatrogenic tardive dyskinesia (TD) is a debilitating and potentially irreversible neurological side effect of chronic treatment with a number

of different types of medication, primarily with antipsychotics (Cornett, Novitch, Kaye, Kata, & Kaye, 2017; Tenback & van Harten, 2011). Typical antipsychotics are associated with higher, 30% incidence of TD, but incidence with atypical antipsychotics is still significant, incapacitating 20% of patients (Cornett et al., 2017; Stegmayer, Walther, & van Harten, 2018). The involuntary movements affect the

*These authors equally contributed to this work.

orofacial area and trunk and limbs, defining orofacial and limb-truncal types of TD. There is no consensus on the pathogenic mechanisms behind these features, and different neurotransmitter systems may be involved, but one of the best known hypotheses postulates that the D2 dopamine receptor (DRD2; Beaulieu & Gainetdinov, 2011) plays an important role (Stegmayer et al., 2018; Zai et al., 2018). Furthermore, the two recently FDA-approved drugs to treat TD, valbenazine and deutetrabenazine, decrease the availability of synaptic dopamine by inhibiting the vesicular monoamine transporter type 2 (Stahl, 2018; Zai et al., 2018), which might also support the hypothesis that DRD2 is implicated in the pathogenesis. According to that hypothesis, blockade by antipsychotics of the inhibitory DRD2 of gamma-aminobutyric acid (GABAergic) medium spiny neurons (MSNs) in the striatum results in compensatory upregulation of a supersensitive type of these receptors, which in turn may lead to excessive inhibition of the GABAergic MSNs that take part in the indirect pathway of the extrapyramidal circuit (Stahl, 2018). This inhibition would result in insufficient inhibition of the cortex with the net result of increased uncontrolled movements. Furthermore, the upregulated supersensitive DRD2 may enhance intracellular cascades that lead to suspected neurodegeneration of GABAergic MSNs of the indirect pathway, which would explain irreversible symptoms in some patients.

Apart from the well-known G protein-dependent DRD2 signaling involving inhibition of cAMP (Beaulieu & Gainetdinov, 2011; Greengard, 2001), another pathway is G protein-independent and involves AKT serine/threonine kinase 1 (AKT1) and glycogen synthase kinase 3 β (GSK3B; Beaulieu, Del'guidice, Sotnikova, Lemasson, & Gainetdinov, 2011; Beaulieu, Gainetdinov, & Caron, 2009; Freyberg, Ferrando, & Javitch, 2010). In the present study, we looked for evidence that supersensitive DRD2s are involved in the pathogenesis of TD, including suspected neurodegeneration of GABAergic MSNs of the indirect pathway, through activation of the G protein-independent DRD2 signaling. In particular, we evaluated association of functional single nucleotide polymorphisms (SNPs) in *AKT1* and *GSK3B* with TD in schizophrenic patients, treated with typical and atypical antipsychotic drugs. The SNPs rs1130214 and rs3730358 in *AKT1* were chosen because of association of the haplotype TC with lower protein levels of AKT1, which suggests impaired mRNA expression or processing (Emamian, Hall, Birnbaum, Karayiorgou, & Gogos, 2004). The variant rs334558, found in the promoter of *GSK3B*, is also known to be functional, because it determines the expression level of *GSK3B*, possibly by regulating transcription factor binding to the promoter (Kwok et al., 2005).

2 | MATERIALS AND METHODS

2.1 | Patients

This study was carried out in accordance with the Code of Ethics of the World Medical Association established for experiments involving humans (Declaration of Helsinki, revised in 2013 (World Medical Association, 2013)). We recruited patients from three psychiatric

hospitals located in Siberian regions of Tomsk, Kemerovo, and Chita in Russia. Each patient provided written informed consent, after the study was approved by the Local Bioethics Committee of the Mental Health Research Institute in Tomsk. None of the participants was compromised in their capacity to consent; therefore, consent from the next-of-kin was not recommended by the ethics committee. The inclusion criteria were a clinical diagnosis of schizophrenia, according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10: F20), and the age of 18–75 years old. Exclusion criteria were non-European ancestry (e.g., Mongol, Buryat, or Khakas origin), pregnancy, any organic brain disorder (such as epilepsy or Parkinson's disease), and relevant pharmacological withdrawal symptoms. To compare antipsychotic medications, all dosages were converted into chlorpromazine equivalents (Andreasen, Pressler, Nopoulos, Miller, & Ho, 2010). Patients were assessed for the presence or absence of TD according to the Abnormal Involuntary Movement Scale (AIMS; Loonen, Doorschot, Hemert, Oostelbos, & Sijben, 2001; Loonen, Doorschot, van Hemert, Oostelbos, & Sijben, 2000; Loonen & van Praag, 2007). AIMS scores for Items 1 to 7 were transformed into a binary form (presence or absence of TD) with Schooler and Kane's criteria (Schooler & Kane, 1982).

2.2 | Genetic analysis

A blood sample was obtained for DNA extraction and genotyping. DNA was extracted from leukocytes in whole peripheral blood using the standard phenol-chloroform method. All genotyping was performed blind to the patient's clinical status.

A total of three SNPs in genes *GSK3B* (rs334558) and *AKT1* (rs3730358 and rs1130214) were genotyped using the fluorogenic 5'-exonuclease TaqMan technology performed on the real-time polymerase chain reaction system "StepOnePlus" (Applied Biosystems, USA).

2.3 | Statistical analysis

Statistical analysis was carried out with SPSS software, release 17. Pearson's chi-squared test was used for the between-group comparison of demographic and clinical parameters, as well as of genotypic and allelic frequencies at significance level $\alpha = 0.05$. Association of genotypes and alleles with TD was also assessed with odds ratios and 95% confidence intervals. Deviation from Hardy-Weinberg equilibrium of genotypic frequencies was also calculated with a chi-squared test. Additionally, one-way analyses of variance of sums of AIMS scores in groups with different genotypes were performed using an *F*-test and Levene's test.

3 | RESULTS

A total of 449 patients with schizophrenia, receiving antipsychotic treatment for more than 3 months, were recruited after obtaining informed consent. According to predefined criteria, 121 patients suffered from TD. Table 1 presents the main demographic and clinical parameters of the studied population. The patients with TD

TABLE 1 Demographic and clinical parameters of the studied patient groups

Parameter	Patients with TD (n = 121)	Patients without TD (n = 328)	p value
Gender			
Men, number of	71 (58.7%)	152 (46.3%)	0.020
Women, number of	50 (41.3%)	176 (53.7%)	
Mean age, years	48 [37.5; 58]	37 [31; 48]	<0.001
Mean age of onset, years	25 [20; 32]	24 [20; 30]	0.974
Mean duration of illness, years	20 [12; 29.5]	11 [5; 18]	<0.001
Mean CPZeq, dose	500 [286.2; 750]	396 [200; 750]	0.021

Note. Range is indicated in square brackets. TD: tardive dyskinesia; CPZeq: chlorpromazine equivalents.

were significantly older, and the duration of schizophrenia in these patients was significantly longer than in patients without TD. Additionally, patients with TD were taking higher doses of antipsychotics. In our sample, TD was diagnosed more often in men than in women.

There was no deviation from Hardy-Weinberg equilibrium. Of the three SNPs tested, neither was associated with TD, when genotypes and alleles were compared between the group of patients with TD and the group without it. Table 2 summarizes these results. Association was also lacking when different types of TD, orofacial (AIMS Items 1 to 4) and limb-truncal (AIMS Items 5 to 7), were considered separately (data not shown). Analyses of variance showed that for all genotypes, the variance in the distribution of sums of AIMS scores is equal, indicating that the severity of TD, for both orofacial and limb-truncal types, is not associated with any of the tested SNPs (data not shown).

4 | DISCUSSION

The G protein-independent DRD2 signaling does not involve cAMP (Beaulieu et al., 2011). In particular, activation of this intracellular cascade results in downregulation of AKT1 that otherwise inhibits GSK3B.

As a result, increased activity of GSK3B is brought by activation of DRD2. These kinases play important roles in many aspects of the life of a cell, such as differentiation, proliferation, metabolism, and survival (Doble & Woodgett, 2003; Dummer & Hemmings, 2007; Emamian, 2012; Frame & Cohen, 2001), including aspects relevant to psychiatric and neurological disorders and response to medication (Beaulieu et al., 2009; Beaulieu et al., 2011; Emamian, 2012; Freyberg et al., 2010; Levchenko et al., 2018). GSK3B is also known to activate apoptosis (Doble & Woodgett, 2003; Frame & Cohen, 2001), which may explain suspected neurodegeneration of GABAergic MSNs of the indirect pathway, resulting in irreversible symptoms in some patients.

Although the studied SNPs are known to alter expression of the DRD2-coupled kinases *AKT1* and *GSK3B*, our study did not find evidence that these variants are associated with antipsychotic-induced TD. In fact, previous studies of *AKT1* and *GSK3B* showed implication of the two kinases in antipsychotic drug action (Beaulieu et al., 2009; Beaulieu et al., 2011; Freyberg et al., 2010), but not in the pathogenesis of TD. In particular, three previous studies that investigated association between two of these SNPs and TD also showed negative results, unless other variables were incorporated into the analyses (Park et al., 2009; Souza et al., 2010; Zai et al., 2008). One of these studies reported association of TD with rs3730358 (*AKT1*) only when taking into account another SNP rs6275, found in *DRD2* (Zai et al., 2008). However, rs6275 was already found to be associated with TD (Zai et al., 2007), so it is unclear to what degree rs3730358 contributes to the reported association. A second study (Park et al., 2009) also reported association with TD only when rs334558 (*GSK3B*) was analyzed together with the Val66Met polymorphism in the brain-derived neurotrophic factor gene (*BDNF*; Miura et al., 2014). The third study reported association of the SNP rs6438552, found in high linkage disequilibrium with rs334558 (*GSK3B*; Kwok et al., 2005), only when age was incorporated as a covariate in the analysis (Souza et al., 2010). Age is the variable known to be robustly associated with TD (Cornett et al., 2017; Tenback & van Harten, 2011; Waln & Jankovic, 2013), so it is unclear to what degree rs6438552 (as a proxy for rs334558) is important in the reported association. As suggested by these studies, *AKT1* and *GSK3B* might play some role in the pathogenesis of antipsychotic-induced TD, possibly via interaction with

TABLE 2 Distribution of alleles and genotypes of *AKT1* and *GSK3B* polymorphisms in groups of patients with TD and patients without TD

Gene	SNP	Genotypes, alleles	Patients with TD	Patients without TD	OR		χ^2	p value
					Value	95% CI		
<i>AKT1</i>	rs3730358	GG	87 (71.9%)	231 (70.6%)	1.06	[0.67, 1.69]	1.178	0.555
		GA	29 (24.0%)	88 (26.9%)	0.86	[0.53, 1.39]		
		AA	5 (4.1%)	8 (2.4%)	1.72	[0.55, 5.36]		
		G	102 (83.9%)	275 (84.1%)	0.98	[0.66, 1.47]		
		A	19 (16.1%)	52 (15.9%)	1.02	[0.68, 1.52]		
	rs1130214	GG	53 (43.8%)	146 (44.6%)	0.97	[0.63, 1.47]	3.136	0.208
		GT	60 (49.6%)	142 (43.4%)	1.28	[0.84, 1.95]		
		TT	8 (6.6%)	39 (11.9%)	0.52	[0.24, 1.15]		
		G	83 (68.6%)	217 (66.4%)	1.11	[0.81, 1.52]		
		T	38 (31.4%)	110 (33.6%)	0.90	[0.66, 1.24]		
<i>GSK3B</i>	rs334558	GG	25 (21.0%)	62 (19.1%)	1.12	[0.67, 1.89]	0.367	0.832
		GA	59 (49.6%)	158 (48.8%)	1.03	[0.68, 1.57]		
		AA	35 (29.4%)	104 (32.1%)	0.88	[0.56, 1.39]		
		G	55 (45.8%)	141 (43.5%)	1.10	[0.81, 1.48]		
		A	64 (54.2%)	183 (56.5%)	0.91	[0.68, 1.23]		

Note. SNP: single nucleotide polymorphism; TD: tardive dyskinesia; OR: odds ratio; CI: confidence interval.

DRD2 and BDNF, but this role seems to be minor (Souza et al., 2010). This conclusion could shed some light on the molecular events taking place in GABAergic MSNs of the striatum and indicate that the downstream activation of GSK3B by superactive DRD2 is not a major factor contributing to the suspected degeneration of these neurons.

The results of our study cannot exclude involvement of the G protein-dependent DRD2 signaling leading to cAMP inactivation (Beaulieu & Gainetdinov, 2011; Greengard, 2001) in the pathogenesis of TD, in a similar manner the G protein-dependent DRD1 signaling leading to cAMP activation is involved in levodopa-induced dyskinesia (Loonen & Ivanova, 2013; Santini et al., 2007). To explore this possibility, additional studies are warranted.

As previously suggested, neurotoxicity brought about by excessive dopamine metabolism could be another possible mechanism of the pathogenesis and the main reason of the neurodegenerative processes in TD (Loonen & Ivanova, 2013). This alternative pathogenic mechanism of TD, unrelated to the upregulated supersensitive DRD2s, could be rooted in formation of toxic molecules, such as dopamine quinines and reactive oxygen species, that are by-products of excessive dopamine metabolism brought about by compensatory increased synaptic concentration of dopamine following blockade of DRD2s by antipsychotics (Cho & Lee, 2013; Cyr et al., 2003; Lohr, Kuczenski, & Niculescu, 2003; Loonen & Ivanova, 2013; Waln & Jankovic, 2013). These molecules may be particularly toxic to the GABAergic MSNs of the indirect pathway that may undergo cell death (Loonen & Ivanova, 2013), which would also explain why the symptoms occur late during treatment and in some patients become permanent. Further investigation of genes that respond to oxidative stress, such as manganese superoxide dismutase (SOD2; Al Hadithy et al., 2010; Zai et al., 2018) and phosphatidylinositol-4-phosphate-5-kinase type IIA (PIP5K2A; Fedorenko et al., 2014), is therefore warranted.

5 | CONCLUSION

This study showed no evidence that AKT1 and GSK3B play a major role in the pathogenesis of antipsychotic-induced TD, despite the important role the two kinases play in the G protein-independent DRD2 signaling. These results support previously reported data and warrant an exploration of other pathogenic mechanisms, such as neurotoxicity due to excessive dopamine metabolism.

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CONFLICTS OF INTEREST

The authors report no conflicts of interest in this work.

ORCID

Anastasia Levchenko <https://orcid.org/0000-0003-3509-1304>

REFERENCES

- Al Hadithy, A. F., Ivanova, S. A., Pechlivanoglou, P., Wilffert, B., Semke, A., Fedorenko, O., ... Loonen, A. J. (2010). Missense polymorphisms in three oxidative-stress enzymes (GSTP1, SOD2, and GPX1) and dyskinesias in Russian psychiatric inpatients from Siberia. *Human Psychopharmacology*, 25(1), 84–91. <https://doi.org/10.1002/hup.1087>
- Andreasen, N. C., Pressler, M., Nopoulos, P., Miller, D., & Ho, B. C. (2010). Antipsychotic dose equivalents and dose-years: A standardized method for comparing exposure to different drugs. *Biological Psychiatry*, 67(3), 255–262. <https://doi.org/10.1016/j.biopsych.2009.08.040>
- Beaulieu, J. M., Del'guidice, T., Sotnikova, T. D., Lemasson, M., & Gainetdinov, R. R. (2011). Beyond cAMP: The regulation of Akt and GSK3 by dopamine receptors. *Frontiers in Molecular Neuroscience*, 4, 38. <https://doi.org/10.3389/fnmol.2011.00038>
- Beaulieu, J. M., & Gainetdinov, R. R. (2011). The physiology, signaling, and pharmacology of dopamine receptors. *Pharmacological Reviews*, 63(1), 182–217. <https://doi.org/10.1124/pr.110.002642>
- Beaulieu, J. M., Gainetdinov, R. R., & Caron, M. G. (2009). Akt/GSK3 signaling in the action of psychotropic drugs. *Annual Review of Pharmacology and Toxicology*, 49, 327–347. <https://doi.org/10.1146/annurev.pharmtox.011008.145634>
- Cho, C. H., & Lee, H. J. (2013). Oxidative stress and tardive dyskinesia: Pharmacogenetic evidence. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 46, 207–213. <https://doi.org/10.1016/j.pnpbp.2012.10.018>
- Cornett, E. M., Novitch, M., Kaye, A. D., Kata, V., & Kaye, A. M. (2017). Medication-induced tardive dyskinesia: A review and update. *The Ochsner Journal*, 17(2), 162–174. <https://doi.org/10.1043/TOJ-16-0108>
- Cyr, M., Beaulieu, J. M., Laakso, A., Sotnikova, T. D., Yao, W. D., Bohn, L. M., ... Caron, M. G. (2003). Sustained elevation of extracellular dopamine causes motor dysfunction and selective degeneration of striatal GABAergic neurons. *Proceedings of the National Academy of Sciences of the United States of America*, 100(19), 11035–11040. <https://doi.org/10.1073/pnas.1831768100>
- Doble, B. W., & Woodgett, J. R. (2003). GSK-3: Tricks of the trade for a multi-tasking kinase. *Journal of Cell Science*, 116(Pt 7), 1175–1186. <https://doi.org/10.1242/jcs.00384>
- Dummler, B., & Hemmings, B. A. (2007). Physiological roles of PKB/Akt isoforms in development and disease. *Biochemical Society Transactions*, 35(Pt 2), 231–235. <https://doi.org/10.1042/BST0350231>
- Emamian, E. S. (2012). AKT/GSK3 signaling pathway and schizophrenia. *Frontiers in Molecular Neuroscience*, 5, 33. <https://doi.org/10.3389/fnmol.2012.00033>
- Emamian, E. S., Hall, D., Birnbaum, M. J., Karayiorgou, M., & Gogos, J. A. (2004). Convergent evidence for impaired AKT1-GSK3 β signaling in schizophrenia. *Nature Genetics*, 36(2), 131–137. <https://doi.org/10.1038/ng1296>
- Fedorenko, O. Y., Loonen, A. J., Lang, F., Toshchakova, V. A., Boyarko, E. G., Semke, A. V., ... Ivanova, S. A. (2014). Association study indicates a protective role of phosphatidylinositol-4-phosphate-5-kinase against tardive dyskinesia. *International Journal of Neuropsychopharmacology*, 18(6), pyu098. <https://doi.org/10.1093/ijnp/pyu098>

- Frame, S., & Cohen, P. (2001). GSK3 takes centre stage more than 20 years after its discovery. *Biochemical Journal*, 359(Pt 1), 1–16. <https://doi.org/10.1042/bj3590001>
- Freyberg, Z., Ferrando, S. J., & Javitch, J. A. (2010). Roles of the Akt/GSK-3 and Wnt signaling pathways in schizophrenia and antipsychotic drug action. *American Journal of Psychiatry*, 167(4), 388–396. <https://doi.org/10.1176/appi.ajp.2009.08121873>
- Greengard, P. (2001). The neurobiology of slow synaptic transmission. *Science*, 294(5544), 1024–1030. <https://doi.org/10.1126/science.294.5544.1024>
- Kwok, J. B., Hallupp, M., Loy, C. T., Chan, D. K., Woo, J., Mellick, G. D., ... Schofield, P. R. (2005). GSK3B polymorphisms alter transcription and splicing in Parkinson's disease. *Annals of Neurology*, 58(6), 829–839. <https://doi.org/10.1002/ana.20691>
- Levchenko, A., Losenkov, I. S., Vyalova, N. M., Simutkin, G. G., Bokhan, N. A., Wilffert, B., ... Ivanova, S. A. (2018). The functional variant rs334558 of GSK3B is associated with remission in patients with depressive disorders. *Pharmacogenomics and Personalized Medicine*, 11, 121–126. <https://doi.org/10.2147/PGPM.S171423>
- Lohr, J. B., Kuczenski, R., & Niculescu, A. B. (2003). Oxidative mechanisms and tardive dyskinesia. *CNS Drugs*, 17(1), 47–62. <https://doi.org/10.2165/00023210-200317010-00004>
- Loonen, A. J., Doorschot, C. H., van Hemert, D. A., Oostelbos, M. C., & Sijben, A. E. (2001). The schedule for the assessment of drug-induced movement disorders (SADiMoD): Inter-rater reliability and construct validity. *International Journal of Neuropsychopharmacology*, 4(4), 347–360. <https://doi.org/10.1017/S1461145701002589>
- Loonen, A. J., Doorschot, C. H., van Hemert, D. A., Oostelbos, M. C., & Sijben, A. E. (2000). The Schedule for the Assessment of Drug-Induced Movement Disorders (SADiMoD): Test-retest reliability and concurrent validity. *International Journal of Neuropsychopharmacology*, 3(4), 285–296. <https://doi.org/10.1017/S1461145700002066>
- Loonen, A. J., & Ivanova, S. A. (2013). New insights into the mechanism of drug-induced dyskinesia. *CNS Spectrums*, 18(1), 15–20. <https://doi.org/10.1017/S1092852912000752>
- Loonen, A. J., & van Praag, H. M. (2007). Measuring movement disorders in antipsychotic drug trials: The need to define a new standard. *Journal of Clinical Psychopharmacology*, 27(5), 423–430. <https://doi.org/10.1097/jcp.0b013e31814f1105>
- Miura, I., Zhang, J. P., Nitta, M., Lencz, T., Kane, J. M., Malhotra, A. K., ... Correll, C. U. (2014). BDNF Val66Met polymorphism and antipsychotic-induced tardive dyskinesia occurrence and severity: A meta-analysis. *Schizophrenia Research*, 152(2–3), 365–372. <https://doi.org/10.1016/j.schres.2013.12.011>
- Park, S. W., Lee, J. G., Kong, B. G., Lee, S. J., Lee, C. H., Kim, J. I., & Kim, Y. H. (2009). Genetic association of BDNF val66met and GSK-3 β -50T/C polymorphisms with tardive dyskinesia. *Psychiatry and Clinical Neurosciences*, 63(4), 433–439. <https://doi.org/10.1111/j.1440-1819.2009.01976.x>
- Santini, E., Valjent, E., Usiello, A., Carta, M., Borgkvist, A., Girault, J. A., ... Fisone, G. (2007). Critical involvement of cAMP/DARPP-32 and extra-cellular signal-regulated protein kinase signaling in L-DOPA-induced dyskinesia. *Journal of Neuroscience*, 27(26), 6995–7005. <https://doi.org/10.1523/JNEUROSCI.0852-07.2007>
- Schooler, N. R., & Kane, J. M. (1982). Research diagnoses for tardive dyskinesia. *Archives of General Psychiatry*, 39(4), 486–487. <https://doi.org/10.1001/archpsyc.1982.04290040080014>
- Souza, R. P., Remington, G., Chowdhury, N. I., Lau, M. K., Voineskos, A. N., Lieberman, J. A., ... Kennedy, J. L. (2010). Association study of the GSK-3B gene with tardive dyskinesia in European Caucasians. *European Neuropsychopharmacology*, 20(10), 688–694. <https://doi.org/10.1016/j.euroneuro.2010.05.002>
- Stahl, S. M. (2018). Mechanism of action of vesicular monoamine transporter 2 (VMAT2) inhibitors in tardive dyskinesia: Reducing dopamine leads to less “go” and more “stop” from the motor striatum for robust therapeutic effects. *CNS Spectrums*, 23(1), 1–6. <https://doi.org/10.1017/S1092852917000621>
- Stegmayer, K., Walther, S., & van Harten, P. (2018). Tardive dyskinesia associated with atypical antipsychotics: Prevalence, mechanisms and management strategies. *CNS Drugs*, 32(2), 135–147. <https://doi.org/10.1007/s40263-018-0494-8>
- Tenback, D. E., & van Harten, P. N. (2011). Epidemiology and risk factors for (tardive) dyskinesia. *International Review of Neurobiology*, 98, 211–230. <https://doi.org/10.1016/B978-0-12-381328-2.00009-2>
- Waln, O., & Jankovic, J. (2013). An update on tardive dyskinesia: From phenomenology to treatment. *Tremor Other Hyperkinet Mov (N Y)*, 3. <https://doi.org/10.7916/D88P5Z71>
- World Medical Association. (2013). World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*, 310(20), 2191–2194. <https://doi.org/10.1001/jama.2013.281053>
- Zai, C. C., Hwang, R. W., De Luca, V., Muller, D. J., King, N., Zai, G. C., ... Kennedy, J. L. (2007). Association study of tardive dyskinesia and twelve DRD2 polymorphisms in schizophrenia patients. *International Journal of Neuropsychopharmacology*, 10(5), 639–651. <https://doi.org/10.1017/S1461145706007152>
- Zai, C. C., Maes, M. S., Tiwari, A. K., Zai, G. C., Remington, G., & Kennedy, J. L. (2018). Genetics of tardive dyskinesia: Promising leads and ways forward. *Journal of the Neurological Sciences*, 389, 28–34. <https://doi.org/10.1016/j.jns.2018.02.011>
- Zai, C. C., Romano-Silva, M. A., Hwang, R., Zai, G. C., Deluca, V., Muller, D. J., ... Kennedy, J. L. (2008). Genetic study of eight AKT1 gene polymorphisms and their interaction with DRD2 gene polymorphisms in tardive dyskinesia. *Schizophrenia Research*, 106(2–3), 248–252. <https://doi.org/10.1016/j.schres.2008.08.036>

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