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BDNF Val66Met polymorphism and antipsychotic-induced tardive dyskinesia occurrence and severity: A meta-analysis

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Abstract

Background—Tardive dyskinesia (TD) is a serious long-term consequence of antipsychotic treatment. Since brain-derived neurotrophic factor (BDNF) has potent neurotrophic activity, genetic alterations in the BDNF gene may affect antipsychotic-induced TD.

Methods—Searching PubMed and Web of Science until 05/31/13, we conducted a systematic review and a meta-analysis of the effects of BDNF Val66Met polymorphism on antipsychotic-induced TD. Pooled odds ratio was calculated to assess the effects of BDNF Val66Met polymorphism on TD occurrence. Additionally, pooled standardized mean differences (Hedges' g) were calculated to assess the effects on Abnormal Involuntary Movement Scale (AIMS) total score.

Results—Out of 699 potentially eligible hits, 6 studies (N = 1740, mean age = 46.0 ± 10.4 years; males = 73.1%; Asians = 80.5%, Caucasians = 19.5%; schizophrenia = 96.2%) were included in this meta-analysis. Pooling data from all studies, no significant associations were found between

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Appendix A. Supplementary data: Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.schres.2013.12.011>.

BDNF Val66Met polymorphism and TD ($p = 0.82$) or AIMS total scores ($p = 0.11$). However, in studies including only Caucasians ($n = 339$), Met allele carriers had significantly higher AIMS total scores (Hedges' $g = 0.253$, 95% confidence interval = 0.030 to 0.476, $p = 0.026$) and non-significantly higher TD occurrence ($p = 0.127$). Conversely, there was no association between BDNF and AIMS scores ($p = 0.57$) or TD ($p = 0.65$) in Asians.

Conclusion—Although there was no significant association between BDNF Val66Met polymorphism and TD or AIMS scores across all patients, our results suggest that BDNF Val66Met polymorphism affects severity and, possibly, TD development in Caucasians. Since the number of studies and patients was still small, additional data are needed to confirm genotype-racial interactions. Furthermore, BDNF enhancing treatments for TD may require further study, especially in Caucasians.

Keywords

Tardive dyskinesia; AIMS; BDNF; Genotype; Schizophrenia; Race

1. Introduction

Tardive dyskinesia (TD) is a severe chronic side effect of antipsychotic treatment. TD sometimes becomes irreversible and has been associated with poor quality of life (Browne et al., 1996; Marsálek, 2000). During treatment with first-generation antipsychotics, annual TD incidence rates are about 5% in adults (Kane et al., 1984; Glazer et al., 1993) and 25–30% in the elderly (Saltz et al., 1991; Jeste et al., 1999). Second-generation antipsychotics have a lower risk for TD than first-generation antipsychotics, with annual incidence rates of 1% or less in adults (Correll et al., 2004; Correll and Schenk, 2008). Nevertheless, TD is still a serious potential problem in the treatment of schizophrenia.

Although the mechanism of TD remains unknown, it has been suggested that up-regulation and hypersensitivity of dopamine D2 receptors (DRD2) in the basal ganglia are associated with TD (Tarsy and Baldessarini, 1977). Therefore, pharmacogenetic studies have been mainly focused on the association between TD and DRD2 genes (Hori et al., 2001; Segman et al., 2003; Liou et al., 2006; Zai et al., 2007) and dopamine D3 receptor (DRD3) genes (Chong et al., 2003; Liou et al., 2004; Zai et al., 2009). A meta-analysis of 4 studies of Taq1A in the *DRD2* found an increased risk for TD to be associated with the A2 allele and A2/A2 genotype compared to the A1 allele (pooled OR = 1.30) and compared to the A1/A1 genotype group (pooled OR = 1.80) (Bakker et al., 2008). Although an earlier meta-analysis of 11 studies reported a significant association between TD and Ser9Gly in the *DRD3* (Bakker et al., 2006), a subsequent meta-analysis of 13 studies showed no significant association anymore (Tsai et al., 2010). Furthermore, another meta-analysis of four studies investigating the relationship between TD and genetic variations in the catechol-O-methyl transferase (COMT) gene that codes for the enzyme degrading dopamine found significant protective effects of the Met–Val heterozygous genotype and Met carrier status (Bakker et al., 2008). Nevertheless, a more recent meta-analysis of 7 studies found a significant association only in one of 6 polymorphisms, and results seemed to be restricted to females (Zai et al., 2010b).

In addition to dopamine receptor dysfunctions, neurotoxicity may also be a mechanism of TD development (Andreassen and Jørgensen, 2000). Antipsychotics (Ho et al., 2011), possibly especially first-generation-antipsychotics, such as haloperidol (Lieberman et al., 2005), may exert neurotoxic effects. For example, long-term antipsychotic treatment induces the synthesis and metabolism of dopamine (Howes and Kapur, 2009), which leads to the production of free radicals. Recent studies suggested that oxidative stress may play an important role for the development of TD (Lohr et al., 2003; Cho and Lee, 2013). On the other hand, prolonged relapses that have been associated with intermittent antipsychotic treatment may also have neurotoxic brain effects (Andreassen et al., 2013).

Based on the oxidative stress hypothesis for TD, studies investigated the association between TD and the NADPH quinone oxidoreductase 1 (NQO1) gene polymorphism that is involved in increased oxidative stress and the manganese superoxide dismutase (MnSOD) gene that codes for the antioxidant enzyme that catalyzes the dismutation of two molecules of the superoxide anion into water and hydrogen peroxide. While a prior meta-analysis of four studies indicated a significant protective effect of the Ala-Val heterozygous genotype and Val carrier status in the MnSOD gene (Bakker et al., 2008), a more recent meta-analysis found no significant associations with TD for either NQO1 (5 studies) or MnSOD gene (9 studies) polymorphisms (Zai et al., 2010a).

Due to its neuroprotective effects that go beyond antioxidant properties, brain-derived neurotrophic factor (BDNF), a member of the “neurotrophin” family of growth factors, has attracted attention relative to the mechanisms involved in TD development and severity. BDNF positively affects neuronal growth, survival, and differentiation (Park and Poo, 2013). BDNF is also a mediator involved in neuronal survival and plasticity of dopaminergic neurons (Angelucci et al., 2005), preventing the spontaneous death (Knüsel et al., 1997) or dopaminergic neuronal damage (Nishio et al., 1998). Furthermore, BDNF protects against reductions in striatal dopamine content by neurotoxins (Hung and Lee, 1996; Angelucci et al., 2005). Notably, several studies found that schizophrenia patients with TD had lower plasma BDNF levels than those without TD (Tan et al., 2005; Yang et al., 2011; Zhang et al., 2012), although Lee et al. (2007) showed no differences between the two groups.

Taken together, accumulating evidence suggests that BDNF may have protective effects on TD development or severity, and that pharmacogenetic studies may be able to uncover a significant relationship between TD and polymorphisms in the BDNF gene. The BDNF gene is located on chromosome 1 p13 and consists of 13 exons. Val66Met is the most studied polymorphism in the BDNF gene, which has been reported to affect human episodic memory and hippocampal neuronal function (Egan et al., 2003) or hippocampal volume (Pezawas et al., 2004). Moreover, Liou et al. (2004) showed a significant association between the Val66Met polymorphism and Abnormal Involuntary Movement Scale (AIMS) orofacial scores in TD patients. However, subsequent studies investigating this polymorphism and TD have shown inconclusive results (Kang et al., 2008; Park et al., 2009; Zai et al., 2009; Wang et al., 2010). Therefore, we performed a meta-analysis to investigate the association between Val66Met polymorphisms in the BDNF gene and TD as well as the

AIMS total score in order to overcome the limitation of small samples and effects in individual studies.

2. Methods

2.1. Search, inclusion criteria, and data extraction

To examine the effects of the BDNF Val66Met polymorphism on TD occurrence and AIMS total score, we conducted a systematic literature review using PubMed and Web of Science until May 31, 2013 with the following keywords: (tardive dyskinesia or TD) and (brain-derived neurotrophic factor or BDNF). To complement the electronic search, we performed a hand search of reference lists of relevant studies and reviews. Furthermore, when required data were missing or not available, we contacted authors for additional and unpublished information. Inclusion criteria for this meta-analysis were: 1) studies investigating the association between Val66Met polymorphism in BDNF and TD or AIMS total score; 2) TD occurred during treatment with antipsychotics; 3) TD was defined using Schooler and Kane (1982) criteria; and 4) allele distribution was in Hardy–Weinberg equilibrium. Two authors (I.M. and C.U.C) checked the inclusion and exclusion criteria, and independently extracted data. Any disagreements were resolved by discussion.

2.2. Statistical analysis

All statistical analyses were performed for dominant (Met carriers vs. Met non-carriers), and recessive (Val carriers vs. Val non-carriers) genetic models. In addition, we compared Met/Met and Val/Val genetic groups, and Met and Val alleles regarding their effect on TD occurrence. Data were entered into and analyzed by Comprehensive Meta-Analysis Version 2.0 (<http://www.meta-analysis.com>; Borenstein et al., 2005). Odds ratios (ORs) with 95% confidence intervals (CI) were used to assess the effects of the BDNF Val66Met genetic variants on TD occurrence. We used random effects model to calculate pooled ORs. For AIMS total score, random effects model was used to combine studies, and Hedges' g was used as the effect size measure for differences between groups. Heterogeneity between studies was tested by using the Q and I^2 statistics, with p value less than 0.05 and I^2 value of 50% or greater indicating significant heterogeneity. In addition to the overall analyses, we performed *a priori* defined subgroup analyses by race, i.e., Asians vs. Caucasians. Furthermore, we performed two exploratory meta-regression analyses using percent male and mean age of the study population as moderator variables. Begg's funnel plot, Egger's test, and the Duval and Tweedie “trim and fill” method were used to explore the possibility of publication bias.

3. Results

3.1. Search results

The electronic search yielded a total of 698 potential studies. In addition, we found 1 study by hand search. Among the 699 identified hits, 12 articles were found to be duplicated between the databases. Of the 687 unique studies, we excluded 669 articles based on title and abstract review. Based on full-text inspection, we excluded another 12 references because of the following reasons: usable data were not reported/obtainable (5 articles: Naoe

et al., 2006; Tsapakis et al., 2006, 2007; Xu et al., 2008,2010); patients were never exposed to antipsychotics (4 articles); the reference was a meeting abstract for the same study included in this meta-analysis (2 articles), the study reported overlapping data for the same study included in this meta-analysis (1 article). Finally, 6 studies including 1740 patients, all focusing exclusively on the BDNF Val66Met polymorphism, were included in this meta-analysis. Supplementary Fig. 1 shows the flowchart of study selection and inclusion.

3.2. Study, patient, and treatment characteristics

Study characteristics are summarized in Table 1. The mean age of the included patients was 46.0 ± 10.4 years, 73.1% were male, 80.5% Asians, 19.5% Caucasians, and 96.2% had a diagnosis of schizophrenia. Four studies included only Asian patients with schizophrenia (Liou et al., 2004; Kang et al., 2008; Park et al., 2009; Wang et al., 2010) and two studies included Caucasian patients with schizophrenia (93.6%) and schizoaffective disorder (6.4%) (Zai et al., 2007) or with schizophrenia (66.7%) and other diagnoses (33.3%) (Bakker et al., 2012). The sample size per study ranged from 161 to 815. Antipsychotics included first-generation antipsychotics in 3 studies, mixed first- and second-generation antipsychotics in 2 studies and one study did not report the type of antipsychotics. The minimum duration of antipsychotic treatment was 3 months in 2 studies, 6 months in 1 study and 12 months in 3 studies. Five of 6 studies used the AIMS and one study used AIMS or Hillside Simpson Dyskinesia Scale to evaluate TD. All studies reported TD frequency and all but one study (Park et al., 2009) reported the total AIMS score for each genotype. The allele distributions of the Val66Met genotype were in Hardy–Weinberg equilibrium in all 6 studies.

3.3. BDNF Val66Met genotype and TD occurrence

Using random effects models, there were no significant associations in the total population between BDNF Val66Met genotype and TD occurrence when comparing Met carriers and Met non-carriers (OR = 1.028, 95%CI = 0.811–1.304, $p = 0.82$; Fig. 1, Table 2), Val carriers and Val non-carriers (OR = 0.938, 95%CI = 0.698–1.260, $p = 0.671$; Table 2), Met/Met genotype and Val/Val genotype (OR = 1.031, 95%CI = 0.762–1.396, $p = 0.841$; Table 2), and Met and Val alleles (OR = 1.024, 95%CI = 0.887–1.183, $p = 0.742$; Table 2). There was no significant heterogeneity in each comparison (Table 2).

In subgroup analyses, there were also no significant associations between TD and any genotype in either Asian or Caucasian study populations and results were also not heterogeneous.

In meta-regression analyses, there were no significant associations between either percent males or mean patient age in the study samples and genotype-related TD risk in the 4 genetic comparisons.

3.4. BDNF Val66Met genotype and TD severity

Using random effects models, there were no significant associations in the total population between BDNF Val66Met genotype and AIMS total score when comparing Met carriers and Met non-carriers (Hedges' $g = 0.094$, 95%CI = -0.020 to 0.209 , $p = 0.105$; Fig. 2, Table 3), Val carriers and Val non-carriers (Hedges' $g = 0.062$, 95%CI = -0.139 to 0.263 , $p = 0.548$;

Table 3), and Met/Met genotype and Val/Val genotype (Hedges' $g = -0.002$, 95%CI = -0.165 to 0.161 , $p = 0.977$; Table 3). Significant heterogeneity was only present in the comparison of Val carriers and Val non-carriers ($p = 0.045$, $I^2 = 59\%$; Table 3).

In Caucasians, significant differences in AIMS total score were found between Met carriers and Met non-carriers (Hedges' $g = 0.253$, 95%CI = 0.030 to 0.476 , $p = 0.026$), Val carriers and Val non-carriers (Hedges' $g = -0.580$, 95%CI = -1.137 to 0.023 , $p = 0.041$), and Met/Met genotype and Val/Val genotype (Hedges' $g = 0.660$, 95%CI = 0.096 to 1.223 , $p = 0.022$). Conversely, there were no significant associations in Asians between BDNF Val66Met genotype and AIMS total score. None of the comparisons by racial subgroup was significantly heterogeneous.

Similar to the findings for TD risk, meta-regression analyses did not reveal any significant associations between percent males and mean age of the study samples and genotype-related AIMS score severity in the 3 genetic comparisons.

3.5. Publication bias

Funnel plot inspection revealed no asymmetry for TD occurrence for any of the four pairwise genotype comparisons depicted in Table 2 (Supplementary Fig. 2 for Met carriers vs. Met non-carriers). However, there was asymmetry regarding the total AIMS score results for the Met carriers vs. Met non-carriers (Egger's test: $p = 0.036$). Using the Duval and Tweedie trim and fill method, two additional unpublished studies were missing for the Met carriers vs. Met non-carriers comparison. After filling in the two missing studies, the genotype effect on AIMS total score remained non-significant (Hedges' $g = 0.051$, 95%CI = -0.093 to 0.1961), with the pooled effect size moving even closer to zero (black diamond in Supplementary Fig. 3). There were too few studies to conduct the same analyses for each racial subpopulation.

4. Discussion

To our knowledge, this is the first comprehensive meta-analysis of the association between the BDNF Val66Met polymorphism and TD. In this meta-analysis of 6 studies with total of 1740 patients, we found no associations between the BDNF Val66Met polymorphism and TD occurrence or TD severity in the entire sample consisting of Asian and Caucasian populations. However, when conducting stratified analyses by race, we did find a significant association between Met non-carriers ($p = 0.026$), Val carriers ($p = 0.041$) and Val/Val genotype ($p = 0.022$) and lower AIMS-rated TD severity in Caucasians, as well as a non-significant result in the same direction of less TD occurrence in Met non-carriers ($p = 0.13$). By contrast, no significant effects were found in studies with Asian populations conducted in Korea and China. In this meta-analysis, one of 6 studies defined the non-TD group as participants with an AIMS total score = 0, whereas 5 studies defined the non-TD group as not fulfilling the Schooler and Kane (1982) criteria. This liberal definition of the non-TD group might lead to a dilution of the genetic effects on TD occurrence. Therefore, it is noteworthy that this meta-analysis investigated genetic effects on not only the categorical TD occurrence but also on the dimensional AIMS total score ratings that take into account scores below and above the threshold of TD caseness defined by the Schooler–Kane criteria.

Notably, consistent with a previous study (Petryshen et al., 2010), the genotype distributions were very different between Asians (Val/Val: 26.6%, Val/Met: 52.7%, Met/Met: 20.7%) and Caucasians (Val/Val: 64.6%, Val/Met: 31.6%, Met/Met: 3.8%). Furthermore, the Met allele exists on different population-specific haplotypes in Europeans and Asians (Petryshen et al., 2010). Thus, this ethnic heterogeneity and, especially lower representation of the Met/Met genotype in Caucasians may explain our different results in Caucasians compared to Asians.

Interestingly, our results of a significant relationship between the non-Met genotype in the BDNF Val66Met polymorphism and TD severity are consistent with findings from a recent study reporting that the improvement of AIMS total scores during randomized placebo-controlled treatment with Ginkgo biloba correlated significantly with increases in serum BDNF levels, and that the improvement was greatest in patients with the Val/Val genotype and lowest with the Met/Met genotype (Zhang et al., 2012). However, this study included only Asian subjects with schizophrenia, which does not allow for a simple comparison with the results in Caucasian populations in our meta-analysis. On the other hand, Met/Met genotype has been associated with antipsychotic treatment resistance (Zhang et al., 2013). Since TD has been associated with treatment refractory schizophrenia (Ascher-Svanum et al., 2008), this finding is consistent with our results of a significant association between the Met genotype and TD severity in Caucasians. Nevertheless, it is also possible that non-adherence due to dyskinetic movements or TD interacts with treatment refractoriness.

The mechanisms underlying TD development during antipsychotic treatment are complex and multiple factors seem to be involved. Although DRD2 gene polymorphisms (Bakker et al., 2008) and, to a degree, COMT gene polymorphisms (Bakker et al., 2008; Zai et al., 2010b) have been associated with TD, results for various enzymes involved in the oxidative stress cascade have been negative. This has included genetic variations in the pro-oxidative stress enzyme NQO1 (Zai et al., 2010a), and the antioxidant enzymes MnSOD (Zai et al., 2010a) and glutathione peroxidase (Shinkai et al., 2006). Although larger studies investigating additional polymorphisms are required to reach more definitive conclusions, these results may indicate that oxidative stress-related genetic polymorphisms may not be predominantly involved in the development of TD during antipsychotic treatment in humans. Since BDNF has functions that go beyond antioxidant effects and since schizophrenia patients with TD were found to have lower BDNF levels than those without TD (Tan et al., 2005; Yang et al., 2011; Zhang et al., 2012), the BDNF Val66Met polymorphism has been the focus of several recent studies. Moreover, the Val66Met substitution has functional importance, affecting intracellular distribution, packaging, and release of the BDNF protein in vitro, and the Met allele has been associated with poorer episodic memory and abnormal hippocampal activation (Egan et al., 2003).

Although we were unable to find a significant association between the BDNF Val66Met polymorphism and TD, our finding that the Met allele was associated with higher TD severity in Caucasians suggests that larger studies of this BDNF polymorphism are needed that are genetically stratified. Further, additional, functionally relevant polymorphisms may exist that affect TD frequency and/or severity. For example, a previous study showed that there were significant interactions between BDNF Val66Met polymorphism and glycogen synthase kinase-3 β polymorphism that were related to the occurrence of TD (Park et al.,

2009). Thus, further studies investigating gene–gene interaction may help to clarify the role of BDNF Val66Met polymorphism for TD. Moreover, further research investigating the relationship between TD and AIMS scores with other BDNF polymorphisms is needed to clarify the association between TD risk and severity and the BDNF gene.

In exploratory meta-regression analyses using percent male and mean age in the study samples as moderator variables, we found no significant associations between these 2 potential moderators and genotype-related TD occurrence or AIMS score-based severity of dyskinetic movements. Although both female sex and older age have been associated clinically with TD risk (Yassa and Jeste, 1992; Jeste et al., 1999), our meta-analytic results regarding the relationship of BDNF Val66Met polymorphism with TD and AIMS severity were independent of sex or age, at least at a study (as opposed to individual patient) level. However, the small number of studies, small sample sizes, narrow age range (mean: 46.0 ± 10.4 years, range: 38.0 ± 10.1 to 48.8 ± 12.4 years) and relatively few female patients (mean: 26.4%, range: 12.4–47.4%) limited the power for the moderator analyses.

There are several limitations in this study. First, we could not include the data of one article and two meeting abstracts because we were unable to obtain data from the authors. Therefore, the number of studies and participants included in this meta-analysis is small. In particular, there were only 2 studies with Caucasian populations and the exploration of moderator variables was limited by the low number of studies and narrow distribution regarding sex and age in the included studies. Second, it is possible that non-genetic factors affected our results. This meta-analysis included patients treated with both first- and second-generation antipsychotics. Second-generation antipsychotics have a lower risk for TD than first-generation antipsychotics (Correll and Schenk, 2008) and also have different effects on BDNF levels (Pillai et al., 2006). The differences in antipsychotic treatment including dose of antipsychotics and duration of antipsychotic treatment might further have affected the results of this meta-analysis. Third, the meta-analysis focused only one BDNF polymorphism, as most studies on TD to date have focused on the BDNF Val66Met polymorphism. Nevertheless, this is the first meta-analysis of the association between antipsychotic-related TD and the BDNF Val66Met polymorphism, which is a biologically plausible TD risk polymorphism. Moreover, our finding of a relationship with the Met allele, at least in Caucasians, suggests that further research on this polymorphism is warranted.

In summary, we found no significant association between the BDNF Val66Met polymorphism and TD occurrence. In Caucasians, however, there was significant association between the BDNF Val66Met polymorphism and AIMS total score, indicating that the Met allele was related to higher TD severity. However, finding needs to be interpreted with caution because of the small sample size of the individual studies and the Caucasian subgroup. Further studies using larger sample sizes are needed to confirm and extend our results, especially in Caucasians. Furthermore, additional studies with a broader age range, more female patients and broad ethnic/racial distributions are needed to clarify to what degree age, sex and race are potential moderators of the genetically conferred risk for TD and severity of dyskinesia in relationship to the Val66Met polymorphism and other polymorphisms in the BDNF gene. Finally, given that dopamine receptor and possibly

COMT gene polymorphisms are involved in TD development studies investigating other genetic risk factors for TD and TD severity and investigating gene–gene interactions may be helpful for clarifying the genetic underpinnings of risk for TD in antipsychotic treated patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Forest plot for the association with BDNF Val66Met polymorphism (Met carriers vs. Met non-carriers) and TD occurrence using random effects model.

Fig. 2.

Forest plot for the association with BDNF Val66Met polymorphism (Met carriers vs. Met non-carriers) and AIMS total score using random effects model.

Table 1
Studies investigating the association between the BDNF val66met polymorphism and antipsychotics-induced tardive dyskinesia.

Study	Ethnicity	Country	Population	Sample size	Mean age (years)	% Male	TD assessment, definition	Non-TD cutoff	AP	Subject	N	Val/Val	Val/Met	Met/Met
Liou et al. (2004)	Asian: 100%	China	SCZ (DSM-IV) patients had received a stable dosage of AP for 6 months	216	47.2 ± 9.6	58.8	AIMS, S-K criteria	AIMS total score = 0	Typical	TD	102	31 (30.4)	42 (41.2)	29 (28.4)
Kang et al. (2008)	Asian: 100%	Korea	SCZ (DSM-IV) patients had received a stable dosage of AP for 3 months	209	45.5 ± 9.7	52.6	AIMS, S-K criteria	Not fulfilling S-K criteria	Typical ^a	TD	83	20 (24.1)	49 (59.0)	14 (16.9)
Park et al. (2009)	Asian: 100%	Korea	SCZ (DSM-IV), inpatients and outpatients had received AP for at least 3 months	161	40.1 ± 6.9	87.6	AIMS, S-K criteria	Not fulfilling S-K criteria	Not reported	TD	83	27 (32.5)	41 (49.4)	15 (18.1)
Zai et al. (2009)	Caucasian: 100%	US and Canada	SCZ (93.6%) and SCZAD (6.4%) (DSM-III-R/IV) patients had received typical AP for at least one year	171	38.0 ± 10.1	64.7	AIMS or HSDS, -K criteria	Not fulfilling S-K criteria	Typical ^a	TD	70	43 (61.4)	26 (37.1)	1 (1.4)
Wang et al. (2010)	Asian: 100%	China	SCZ (DSM-IV), with at least 5 years of illness, had received stable doses of AP for at least 12 months	815	48.1 ± 9.6	84.4	AIMS, S-K criteria	Not fulfilling S-K criteria	Mixed	TD	333	86 (25.8)	178 (53.5)	69 (20.7)
Bakker et al. (2012)	Caucasian: 100%	Netherlands	SCZ (66.7%) and other diagnosis (DSM-IV), inpatients had a history of cumulative AP intake of minimally 1 year	168	48.8 ± 12.4	58.8 ^b	AIMS, S-K criteria	Not fulfilling S-K criteria	Mixed	TD	49	26 (53.1)	19 (38.8)	4 (8.2)
N = 4	Asian: 100%	China: N = 2; Korea: n = 2	SCZ: 100%	1401	46.7 ± 9.7	76.1	AIMS: N = 4, S-K criteria: N = 4	Not fulfilling S-K criteria: N = 3; AIMS total score = 0: N = 1	Typical: N = 2; mixed: N = 2; not reported: N = 1	TD	601	164 (27.3)	310 (51.6)	127 (21.1)
N = 2	Caucasian: 100%	Netherlands: n = 1; US and Canada: n = 1	SCZ: 80.2%	339	43.4 ± 12.5	61.5	AIMS: N = 1; AIMS or HSDS: N = 1, S-K criteria: N = 2	Not fulfilling S-K criteria	Typical: N = 1; mixed: N = 1	TD	119	69 (58.0)	45 (37.8)	5 (4.2)
Total: N = 6	Asian (80.5%);Caucasian(19.5%)	China: n = 2; Korea: n = 2; Netherlands: n = 1; US and Canada: n = 1	SCZ: 96.2%; AP use mo: N = 3; 6 mo: N = 1, 3 mo: N = 2	1740	46.0 ± 10.4	73.1	AIMS: N = 5; AIMS or HSDS: N = 1, S-K criteria: N = 6	Not fulfilling S-K criteria: N = 5; AIMS total score = 0: N = 1	Typical: N = 3; mixed: N = 2; not reported: N = 1	TD	720	233 (32.4)	355 (49.3)	132 (18.3)
										Non-TD	1020	358 (35.1)	491 (48.1)	171 (16.8)

Abbreviations: SCZ, schizophrenia; SCZAD, schizoaffective disorder; AP, antipsychotics; TD, tardive dyskinesia; AIMS, Abnormal Involuntary Movement Scale; HSDS, Hillside Simpson Dyskinesia Scale; S-K criteria, Schooler and Kane criteria.

^a All subjects received typical antipsychotics, but included patients who received both typical and atypical antipsychotics.
^b Abstracted from sample group (n = 194) which included non-white patients.

Table 2

Meta-analysis of the association between BDNF Val66Met polymorphism and TD.

Comparisons of genetic groups	Subjects	Sample size		No. of studies	Association		Test of heterogeneity				
		TD	Non-TD		Random model		Q value	p value	I ² (%)		
					OR (95%CI)	Z value				p value	
Met carriers vs. Met non-carriers	Overall	720	1020	6		1.028 (0.811, 1.304)	0.028	0.820	0.145	39	
	Asian	601	800	4		0.942 (0.726, 1.223)	-0.447	0.655	3.281	0.350	8.6
	Caucasian	119	220	2		1.561 (0.881, 2.764)	1.527	0.127	1.506	0.220	33.6
Val carriers vs. Val non-carriers	Overall	720	1020	6		0.938 (0.698, 1.260)	-0.425	0.671	4.145	0.529	0
	Asian	601	800	4		0.955 (0.704, 1.296)	-0.294	0.769	3.571	0.312	16
	Caucasian	119	220	2		0.724 (0.229, 2.294)	-0.549	0.583	0.364	0.546	0
Met/Met vs. Val/Val	Overall	365	529	6		1.031 (0.762, 1.396)	0.201	0.841	3.672	0.598	0
	Asian	291	371	4		0.996 (0.728, 1.362)	-0.027	0.979	2.406	0.493	0
	Caucasian	74	158	2		1.694 (0.524, 5.474)	0.88	0.379	0.531	0.466	0
Met vs. Val	Overall	1440	2040	6		1.024 (0.887, 1.183)	0.329	0.742	6.762	0.239	26.1
	Asian	1202	1600	4		0.992 (0.854, 1.154)	-0.099	0.921	2.386	0.496	0
	Caucasian	238	440	2		1.423 (0.877, 2.309)	1.429	0.153	1.542	0.214	35.1

Table 3

Meta-analysis of the association between BDNF Val66Met polymorphism and AIMS total score.

Comparisons of genetic groups	Subjects	Sample size	No. of studies	Association		Test of heterogeneity			
				Random model	Q value	p value	I ² (%)		
				Hedges' g (95%CI)	Z value	p value			
Met carriers vs. Met non-carriers	Overall	1465	5	0.094 (−0.020, 0.209)	1.623	0.105	4.589	0.332	12.8
	Asian	1126	3	0.038 (−0.095, 0.171)	0.56	0.576	1.612	0.447	0
	Caucasian	339	2	0.253 (0.030, 0.476)	2.229	0.026	0.322	0.570	0
Val carriers vs. Val noncarriers	Overall	1465	5	0.062 (−0.139, 0.263)	0.6	0.548	9.763	0.045	59
	Asian	1126	3	0.158 (−0.058, 0.373)	1.435	0.151	3.286	0.193	39.1
	Caucasian	339	2	−0.580 (−1.137, 0.023)	−2.042	0.041	0.919	0.338	0
Met/Met vs. Val/Val	Overall	764	5	−0.002 (−0.165, 0.161)	−0.029	0.977	7.873	0.096	49.2
	Asian	532	3	−0.063 (−0.233, 0.107)	−0.724	0.469	1.247	0.536	0
	Caucasian	232	2	0.660 (0.096, 1.223)	2.295	0.022	0.834	0.361	0