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Systematic review and meta-analysis of serotonin transporter genotype and discontinuation from antidepressant treatment

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Abstract
There is evidence that 5-HTTLPR is associated with response following treatment from selective serotonin reuptake inhibitors (SSRIs). The short (S) allele has reduced serotonin transporter expression, compared to the long (L) allele, and has been reported to be associated with poorer response in Europeans, with the effect in other populations unclear. However the published literature is inconsistent. A systematic review and meta-analysis was performed to investigate the effect of 5-HTTLPR on discontinuation from antidepressant treatment. Data were obtained from 17 studies including 4309 participants. The principal outcome measure was the allelic odds ratio (*OR*) for the 5-HTTLPR S allele and discontinuation status. A random effects meta-analysis provided no evidence that the S allele was associated with increased odds of discontinuation from SSRIs in Europeans (*OR* 1.09, 95% CI 0.83–1.42, p=0.53; 10 studies, n=2504) but in East Asians there was evidence of a reduced odds of discontinuation (*OR* 0.28, 95% CI 0.12–0.64, p=0.002; 2 studies, n=136). There was a suggestion of small study bias (p=0.05). This meta-analysis provides no evidence of an association between 5-HTTLPR and discontinuation from antidepressant treatment in Europeans. The low number of studies in East Asian samples using SSRIs reduces confidence in our evidence that the S allele decreases the odds of discontinuation in this population. At present, there is no evidence of an association between 5-HTTLPR and discontinuation from SSRI treatment in a European population with further studies required to investigate its effects in different populations.

1. Introduction

Antidepressants are frequently prescribed in the treatment of depression. However, long-term treatment is required for antidepressants to successfully alleviate the symptoms of depression. Individuals who stop antidepressant treatment prematurely may not benefit from treatment and are at a higher risk of relapse (Montgomery et al., 1993; Donoghue et al., 1996). The most common reasons for early discontinuation from antidepressant treatment are adverse effects and lack of efficacy (Demyttenaere et al., 2001). It is not currently possible to accurately predict who will discontinue treatment.

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Variability in antidepressant response has been shown to be influenced by both genetic and environmental factors (Uher, 2008) creating the possibility of using genetic biomarkers capable of predicting discontinuation from treatment.

Selective serotonin reuptake inhibitors (SSRIs) are the first choice antidepressant due to their superior adverse effect profile. SSRIs increase the levels of serotonin in the synaptic cleft by binding to the serotonin reuptake transporter (5-HTT), preventing the reuptake and subsequent storage or degradation of serotonin. This leads to the accumulation of serotonin in the synaptic cleft, which in turn may cause adaptive changes in both serotonergic and noradrenergic neurotransmission and downstream neural adaptation, helping to alleviate the symptoms of depression (Hashimoto, 2009; Vidal et al., 2009). SSRI-induced side effects may occur when levels of synaptic serotonin increase to an intolerably high concentration resulting in over-stimulation of serotonin receptors in the brain and periphery (Ferguson, 2001).

The serotonin transporter gene-linked polymorphic region (5-HTTLPR) modulates transcriptional activity of 5-HTT. 5-HTTLPR is a 44 base pair insertion–deletion polymorphism which can exist as a long (L) variant of a 16 repeat sequence or a short (S) variant of 14 repeats. The L allele is associated with higher levels of transcription *in vitro* compared to the S allele (Lesch et al., 1996). Therefore, the same dose of SSRI may inhibit a higher proportion of 5-HTT in individuals carrying the S allele, causing a rapid accumulation of synaptic serotonin and increasing the risk of adverse effects, potentially leading to discontinuation. As studies have associated 5-HTTLPR with mood disorder (Bellivier et al., 1998; Hauser et al., 2003; Joiner et al., 2003) and unipolar depression (Clarke et al., 2010) it is important to distinguish between genuine pharmacogenetic effects as opposed to effects which simply reflect genotype acting as a marker for disease severity.

The association between 5-HTTLPR and antidepressant treatment has been subject to numerous studies with the majority investigating the outcome of response. In general, data on the number of discontinuations is collected but rarely published with regards to 5-HTTLPR. Murphy et al. (2004) found that discontinuation rates due to adverse effects were lower in patients of European ancestry receiving paroxetine who were L/L homozygotes. Several studies have reported that patients with an S allele more frequently experience adverse effects during treatment with SSRIs than L allele carriers (Perlis et al., 2003; Maron et al., 2009; Kato and Serretti, 2010). The largest study to date, using the STAR*D cohort, reported that a lesser burden of adverse effects from citalopram treatment was associated with the L allele (Hu et al., 2007). However, the authors reported no evidence of an association between 5-HTTLPR and intolerance (discontinuation with high adverse effect score) to citalopram. The second largest study to date, using the Genome Based Therapeutic Drugs for Depression (GENDEP) cohort, found no evidence of an association between 5-HTTLPR genotype and adverse effects, self-reported adherence or discontinuation with escitalopram or nortriptyline (Huezo-Diaz et al., 2009). Other studies have also failed to find evidence of an association between 5-HTTLPR variants and adverse reactions induced by various SSRIs including fluvoxamine (Takahashi et al., 2002; Kato et al., 2006), paroxetine (Kato et al., 2005; Tanaka et al., 2008) and sertraline (Ng et al., 2006) or have even reported the SS genotype to be associated with lower rates of agitation compared to those with SL/LL genotype (Kronenberg et al., 2007).

These contradictory findings have possibly occurred because studies *in vivo* have not consistently reported the L allele to be associated with an increase in transporter binding sites (Murthy et al., 2010). Other polymorphisms have also been reported to influence gene expression, in particular a single nucleotide polymorphism within the L allele (rs25531). This L_G allele may be associated with reduced transporter expression, in a similar manner to the S allele (Hu et al., 2006). Additionally, the role of ancestry may be important. There is a much higher frequency of the S allele in East Asian (79%) than in European (42%) populations (Kunugi et al., 1997). The difference in allele frequency has the potential to introduce confounding by population structure, as well as reducing the power in studies where the allele frequency is lower. In addition differences in linkage disequilibrium patterns between populations may be important if the SNP which is being studied is a proxy for the one which is influencing outcome.

There have been several meta-analyses attempting to clarify the role of 5-HTTLPR in response to antidepressant treatment. The most recent meta-analysis, which included 33 studies (5479 subjects), concluded that in Europeans 5-HTTLPR may be a predictor of antidepressant response and remission, while in East Asians it does not appear to play a major role (Porcelli et al., 2012). An earlier meta-analysis which included 28 studies (5408 subjects) concluded that the 5-HTTLPR bi-allelic short/long polymorphism by itself does not seem to predict antidepressant response to a clinically useful degree (Taylor et al., 2010). These conflicting findings may be due to the inclusion of different studies as well as stratifying by different factors. A meta-analysis of 9 studies with 2642 participants found that the L allele was associated with a reduced risk of experiencing side effects (Kato and Serretti, 2010).

To build on the work of previous meta-analyses we decided to investigate the association between 5-HTTLPR and the number of individuals who discontinue antidepressant treatment. Our outcome of discontinuation includes individuals who discontinued antidepressant treatment for any reason. We chose our outcome of discontinuation as it does not require an individual to make a potentially complex psychosocial judgement on the reason of discontinuation. Additionally, examining discontinuation is often used to study comparative acceptability of medication (Cipriani et al., 2009). Ideally our hypothesis would be tested by studying rates of adverse effects but unfortunately not all studies collect this data and exclusion of these studies could introduce bias. Our choice of outcome is clinically important as individuals who discontinue prematurely from antidepressant treatment are unable to benefit from the treatment and are at greater risk of relapse (Montgomery et al., 1993; Donoghue et al., 1996). To our knowledge this is the first meta-analysis to use an outcome of discontinuation from antidepressant treatment.

2. Experimental Procedures

2.1. Selection of studies for inclusion

Studies in which depressed individuals received antidepressant medication and data on discontinuations were reported by 5-HTTLPR

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