European Neuropsychopharmacology (2013) **23**, 555–560

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Pharmacogenetics of response to methylphenidate in adult patients with Attention-Deficit/Hyperactivity Disorder (ADHD): A systematic review

Verônica Contini[a,b], Diego L. Rovaris[c], Marcelo M. Victor[a], Eugenio H. Grevet[a], Luis A. Rohde[a,b], Claiton H.D. Bau[c,*]

[a]*ADHD Outpatient Clinic, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil*
[b]*National Institute of Developmental Psychiatry for Children and Adolescents, Brazil*
[c]*Departament of Genetics, Instituto de Biociências, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil*

Received 15 February 2012; received in revised form 8 May 2012; accepted 13 May 2012

KEYWORDS
Attention-Deficit/Hyperactivity Disorder;
ADHD;
Pharmacogenetics;
Methylphenidate;
Pharmacogenomics;
Genetics

Abstract
Methylphenidate (MPH) is a first line option in the psychopharmacologic treatment of adults with Attention-Deficit/Hyperactivity Disorder (ADHD). However, there is a considerable proportion of adult patients who do not respond to treatment with MPH or discontinue drug therapy. Since effects of genetic variants in the response to MPH treatment might explain these negative outcomes, we conducted an electronic systematic search of MEDLINE-indexed literature looking for articles containing information about pharmacogenetics of ADHD in adults published until January, 2012. The keywords used were 'ADHD', 'Attention-Deficit/Hyperactivity Disorder' and 'gene' in combination with methylphenidate, amphetamine or atomoxetine. Only 5 pharmacogenetic studies on adult ADHD met inclusion criteria. The results evidenced that most findings obtained so far are negative, and all studies focused on MPH response. There is only one positive result, for a polymorphism at the dopamine transporter gene (*DAT1*) gene. The current state of the art in adult ADHD implies that pharmacogenetic tests are far from routine clinical practice. However, the integration of these studies with neuroimaging and neuropsychological tests may help to understand mechanisms of drug action and the pathophysiology of ADHD.

1. Introduction

Although Attention-Deficit/Hyperactivity Disorder (ADHD) was seen as a childhood disorder in the past, robust evidences document its persistence into adolescence and adulthood in the last decade. In the mid-1960s prospective studies demonstrated that ADHD symptoms persist with phenotypic changes but still with functional impairment

*Correspondence to: Departamento de Genética, Instituto de Biociências, UFRGS, CEP 91501-970, Caixa Postal 15053, Porto Alegre, RS, Brazil. Tel.: +5551 3308 6718; fax: +5551 3308 7311.
E-mail address: claiton.bau@ufrgs.br (C.H.D. Bau).

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http://dx.doi.org/10.1016/j.euroneuro.2012.05.006

(Menkes et al., 1967). Based on this evidence, Wood et al. (1976) tested methylphenidate (MPH), the drug of choice in children and adolescents, in adults. Their positive results were then replicated in more than 20 randomized controlled trials (RCT) in adults, including immediate and extended release formulations. Its efficacy and safety were also confirmed in meta-analytic studies (Castells et al., 2011; Faraone et al., 2004; Koesters et al., 2009) and MPH became the first choice in psychopharmacologic treatment in adults with ADHD (Nutt et al., 2007). However, in spite of the fact that most of the patients with ADHD treated with MPH experience significant improvements, there is a considerable proportion of patients who do not respond to treatment or discontinue drug therapy, making the response to MPH quite variable and difficult to predict (Wigal, 2009).

Efforts have been made in order to better understand the predictors of MPH treatment response among adults with ADHD. Considering clinical aspects, an important source of variation are the predictors of premature termination before (pretreatment attrition) and during (dropout) the treatment. Victor et al. (2009), in a naturalistic study of immediate-release MPH (IR-MPH), verified that current diagnoses of alcohol abuse, obsessive–compulsive, bipolar and oppositional defiant disorders are associated with pretreatment attrition, while current social phobia is associated with dropout. Interestingly, demographic factors and ADHD severity did not reveal influences in premature termination of the treatment. On the other hand, Buitelaar et al. (2009), in a RCT of long-acting MPH, found that higher baseline severity scores were a strong predictor of superior response. In addition, male gender and lower academic achievement were also positive predictors for certain outcomes of treatment response (Buitelaar et al., 2009). Despite demographic and clinical information have provided some contribution to the prediction of treatment response, the translation of these findings to the clinical world has not being evident, raising expectations that pharmacogenetic studies could add more information.

Pharmacogenetics is the study of the genetic factors that influence drug effectiveness and toxicity (Mroziewicz and Tyndale, 2010; Weinshilboum, 2003). At the present time, tens of millions of single nucleotide polymorphisms (SNPs) have been identified in the human genome (dbSNP, http://www.ncbi.nlm.nih.gov/projects/SNP/snp_summary.cgi), besides thousands of insertions, deletions and variable number of tandem repeat (VNTR) polymorphisms. The idea that a lot of these variations can be involved with pharmacological response has resulted in the publication of many associations and functional studies assessing the effects of polymorphisms in genes of enzymes, receptors, transporters, or other targets on drug effectiveness and adverse effects (Johnson, 2010; Manolopoulos et al., 2010; Verde et al., 2010; Yee et al., 2010).

So far, most of the pharmacogenetic investigations in ADHD patients have focused on MPH response and were conducted in children samples (Froehlich et al., 2010; Kieling et al., 2010). Considering that MPH therapeutic effects are mainly related to the catecholamine neurotransmission in the prefrontal cortex (Arnsten and Pliszka, 2011; Wilens, 2008), pharmacogenetic studies have investigated genes involved in this pathway as the primary candidate for investigations. The first and the most studied gene is the dopamine transporter gene (*SLC6A3*, *DAT1*), given that MPH mechanism of action includes the blockade of dopamine transporters (Wilens, 2008; Winsberg and Comings, 1999). In children, a meta-analysis of *DAT1* effects on MPH response showed a significant association between the 10–10 genotype of a VNTR in the 3-untranslated region (3′-VNTR) and low rates of MPH response (Purper-Ouakil et al., 2008). However, since this preliminary meta-analysis, other *DAT1* studies were published and this association is still on debate. In fact, since then, several other genes have been associated with MPH response in children indicating that the variability in clinical response is probably influenced by multiple genes of small effects (Froehlich et al., 2010; Kieling et al., 2010; Polanczyk et al., 2010). Unfortunately, the available literature on pharmacogenetic investigations in adult ADHD is much scarcer. In this study, we review and discuss the findings on pharmacogenetic studies in adults.

2. Experimental procedures

A literature search was conducted in MEDLINE via PubMed database (http://www.ncbi.nlm.nih.gov/). We looked for articles containing information about pharmacogenetics of ADHD published until January, 2012. The search was limited to studies including humans and in English language. The keywords used were ‘ADHD’, ‘Attention-Deficit/Hyperactivity Disorder’ and ‘gene’ in combination with methylphenidate, amphetamine or atomoxetine. Articles that met the following inclusion criteria were selected: dealt with adults patients; assessed effect of methylphenidate, amphetamine or atomoxetine; used DSM-IV or ICD-10 for the diagnosis of ADHD; used a genome-wide or candidate-gene association approach; defined *a priori* a criterion of response.

In the first step 99 articles were identified using the keywords cited above in combination with methylphenidate, of which 35 were pharmacogenetic studies. Only 4 studies involved adult patients. In a second step the references and ‘related citations’ of these four articles were checked. No additional work was found. In addition, we included an article in press from our own group and contacted the main authors of the other selected studies to look for in press data relevant for the topic of this review (Figure 1). The search for

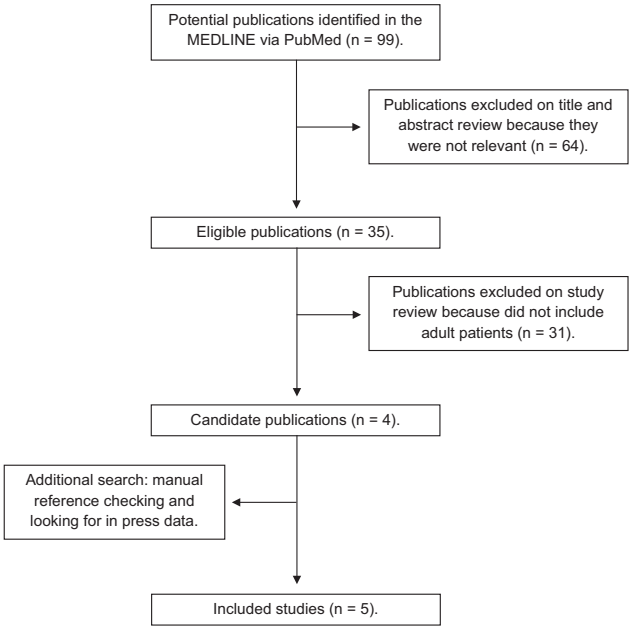

Figure 1 Selection of studies included in the systematic review.

amphetamine and atomoxetine did not result in studies after the first step.

3. Results

There are four published and one in press pharmacogenetic studies in adult ADHD. Considering these investigations, 10 genes were evaluated: *DAT1*, dopamine D4 receptor gene (*DRD4*), norepinephrine transporter gene (*SLC6A2*, *NET1*), adrenergic α2A receptor gene (*ADRA2A*), serotonin 1B receptor gene (*HTR1B*), serotonin transporter gene (*SLC6A4*, *5-HTT*), tryptophan hidroxylase-2 gene (*TPH2*), dopamine beta hidroxilase gene (*DBH*), catechol-O-methyltransferase gene (*COMT*) and the synaptosomal-associated protein 25 gene (*SNAP25*) (Table 1).

The first investigation was performed in the United States by Mick et al. (2006). The authors genotyped the 3′-VNTR polymorphism at *DAT1* gene in 106 patients enrolled in a RCT study of MPH treatment (66 MPH and 40 placebo subjects). The results evidenced that subjects homozygous for the 10-repeat allele were not distinguished from heterozygous 9/10 or homozygous 9-repeat allele in level of symptom reduction (as measured by the change from baseline in the Adult ADHD Investigator System Report Scale—AISRS), dose required for response, cardiac side effects or spontaneously reported adverse effects.

Kooij et al. (2008) investigated polymorphisms at *DAT1* (3′-VNTR), *DRD4* (120-bp tandem insertion/deletion upstream of exon 1 and 48-pb VNTR of exon 3) and *NET1* (4-bp insertion/deletion in the promoter region) genes in 42 adults treated with IR-MPH. Although the original study was a RCT study, there was no placebo arm in the pharmacogenetic analysis. The primary study outcome was clinical response, defined *a priori* as a decrease of at least 2 points on the Investigator-based Clinical Global Impression-Severity scale for ADHD (CGI-S), as well as a 30% or greater symptom reduction as measured with the self-reported DSM-IV ADHD-rating scale (ADHD-RS). The two secondary measures of response were the same scales, taken separately. No significant associations were found between any investigated polymorphisms and the primary outcome of treatment response. However, when the CGI-S and ADHD-RS scales were evaluated separately, patients homozygous for the 10-repeat allele of the 3′-VNTR polymorphism at *DAT1* were less likely to present clinical response in comparison with patients carriers of a single 10-repeat allele for the ADHD-RS, but not for the CGI-S.

Studies conducted by our group focused initially on polymorphisms at *DAT1* (rs2652511, 30-bp VNTR of intron 8 and 3′-VNTR) (Contini et al., 2010) and *ADRA2A* (rs1800544, rs1800545 and rs553668) (Contini et al., 2011) genes, with no association. Negative associations were also found for another 11 polymorphisms in 7 genes (*HTR1B*, *5-HTT*, *TPH2*, *DBH*, *DRD4*, *COMT* and *SNAP25*) (Contini et al., in press). These studies were naturalistic and investigated almost 200 patients, treated with IR-MPH. The outcome measures of MPH response were the Portuguese version of the Swanson, Nolan, and Pelham Rating Scale version IV (SNAP-IV) and the CGI-S scale. The final measurements were taken after the 30th day of treatment and the *a priori* definition of clinical response was a 30% or greater symptom reduction in SNAP-IV and a CGI-S score of two points or less.

A detailed description of the methodological aspects of pharmacogenetic studies of adult ADHD is presented in Table 1.

4. Discussion

This review evidenced that most findings in the pharmacogenetics of adult ADHD obtained so far are negative, and all of the studies focused on the response to MPH. There is only one positive result, for a polymorphism at *DAT1* gene. However, perhaps the most important observation is that few studies were conducted in this field, and no investigations have focused on other drugs that are used to treat ADHD (e.g. atomoxetine, amphetamine).

Further studies considering multiple alleles of multiple genes are needed before fully understanding the potential and implications of genetic variability in the treatment of adults with ADHD. It is important to draw attention to some methodological aspects that should be considered in the interpretation of the available evidence. First of all, several genes were investigated only once and by the same group (Contini et al., in press, 2011, 2010). In addition, sample sizes are small; only one study included a placebo arm in the pharmacogenetic analysis (Mick et al., 2006) and there is also variability in the definition and measures of response, in the clinical dichotomization of the patients (e.g. responders vs. non-responders) and in the assessment of potential confounders (e.g. comorbidities). All these factors are likely to add more heterogeneity into the studies, making more difficult to find a genetic effect. However, a significant pharmacogenetic finding, to be cost-effective, should be significant despite the heterogeneity that is common in clinical settings.

The comorbidity profile of adults with ADHD, which is quite different from children (e.g. high prevalence of substance use disorders in adults), may be related to the difficulty in identifying genetic variants associated with MPH response. In the case of nicotine use, for example, it has been hypothesized that patients with ADHD might use nicotine as a relief for attentional deficits (Gehricke et al., 2007, 2006Levin et al., 1998), which could be influencing some measures of MPH response. Besides that, substance use disorders were also associated with a reduced MPH response (Castells et al., 2011). Actually, a substantial proportion of adult patients do not present good treatment compliance, which may be associated with the presence of some comorbidities (Victor et al., 2009), and this preliminary step might also represent an important source of genetic heterogeneity that has not been explored so far.

Indeed, several aspects of response to MPH demand more investigation. For example, few pharmacogenetic studies addressed adverse event risk and the tolerability of MPH, which could be clinically more relevant. In adults, only one study investigated the possible effect of *DAT1* gene on cardiac parameters and on spontaneously reported adverse effects (Mick et al., 2006). Although the authors found no consistent statistical evidence of any association with *DAT1* genotypes on these variables, they found a 16-point increase in systolic blood pressure in a small group of subjects homozygous for the 9-repeat allele (N=6). This particular finding may indicate that individuals with the 9/9-repeat genotype are at greatest risk for adverse

Table 1 Pharmacogenetic studies assessing MPH response in adults with ADHD.

Gene/ polymorphism	Design/sample	Medication/ dose	Primary outcome	Results	Reference
DAT1 3′-VNTR	RTC, 6-week, *n*=106, American subjects (66 MPH and 40 Placebo)[a]	IR-MPH, OROS-MPH, forced-titration: 0.5-1.0 mg/kg/day	Reduction in AISRS	No association	Mick et al. (2006)
DAT1 3′-VNTR ***NET*** 4-bp ins/del ***DRD4*** 120-bp ins/del 48-bp VNTR	RTC[b], 3-week, *n*=42, Dutch subjects. Mean age=42.5 years (range 20.1-55.7)	IR-MPH, forced-titration: 0.5-1.0 mg/kg/day	≥30% symptom reduction in ADHD-RS plus a CGI-S score of two points or less	Patients homozygous for the 10-repeat allele (*DAT1*) were less likely to present clinical response when compared with patients carriers of a single 10-repeat allele. No association with *NET1* and *DRD4* polymorphisms	Kooij et al. (2008)
DAT1 rs2652511 Int8 VNTR 3′-VNTR	Naturalistic, 4-week, *n*=171 Brazilian of European descent. Mean age=35±11 years	IR-MPH, >0.3 mg/kg/day	≥30% symptom reduction in SNAP-IV plus a CGI-S score of two points or less	No association	Contini et al. (2010)
ADRA2A rs1800544 rs1800545 rs553668	Naturalistic, 4-week, *n*=165, Brazilian of European descent. Mean age=35±11 years	IR-MPH, >0.3 mg/kg/day	≥30% symptom reduction in SNAP-IV plus a CGI-S score of two points or less	No association	Contini et al. (2011)
HTR1B rs11568817 rs6296 rs13212041 ***SLC6A4*** 5-HTTLPR ***TPH2*** rs1843809 rs4570625 ***DBH*** rs1611115 ***DRD4*** 48-bp VNTR ***COMT*** rs4680 ***SNAP25*** rs3746544 rs363020	Naturalistic, 4-week, *n*=164, Brazilian of European descent. Mean age=35±11 years	IR-MPH, >0.3 mg/kg/day	≥30% symptom reduction in SNAP-IV plus a CGI-S score of two points or less	No association	Contini et al. (in press)

DAT1, dopamine transporter gene; VNTR, variable number of tandem repeats polymorphism; *NET*, norepinephrine transporter gene; *DRD4*, dopamine D4 receptor gene; *ADRA2A*, adrenergic 2A receptor gene; *HTR1B*, serotonin 1B receptor gene; *SLC6A4*, serotonin transporter gene; 5-HTTLPR, serotonin transporter gene-linked polymorphic region; *TPH2*, tryptophan hidroxylase-2 gene; *DBH*, dopamine beta hidroxilase gene; *COMT*, catechol-O-methyltransferase gene; *SNAP25*, synaptosomal-associated protein 25 gene; RTC, randomized placebo-controlled trial; IR-MPH, immediate-release methylphenidate; OROS-MPH, methylphenidate extended release; AISRS, the Adult ADHD Investigator System Report Scale; ADHD-RS, DSM-IV ADHD rating scale; SNAP-IV, Swanson, Nolan and Pelham Rating Scale-version IV; CGI-S, Clinical Global Impression Severity Scale.

[a]Mean age not informed for the total sample (inclusion criterion: between 19 and 60 years old).

[b]No placebo arm in the pharmacogenetic analysis.

cardiovascular effects and can only tolerate lower doses. However, the number of subjects with the 9/9-repeat was very small and larger studies would be necessary to confirm this hypothesis.

Despite the limited findings from the pharmacogenetic investigations of adult ADHD, the discovery of genetic variants with strong effects on MPH response is not expected, as evidenced by pharmacogenetic findings in children samples (Mick et al., 2008; Polanczyk et al., 2010). In this sense, the utility of the use of small effect genes might be questioned in terms of application to clinical practice, especially considering the large effect sizes

attributed to ADHD stimulant treatment (Castells et al., 2011; Wigal, 2009). A major goal of clinical pharmacogenetics is to establish phenotype–genotype associations through genetic tests, which is particularly challenging to achieve for complex diseases involving multiple genes. The scarcity of pharmacogenetic applications is not limited to ADHD, but also to drug therapy in general (Ma and Lu, 2011). If the clinical application is still awaited, a more optimistic perspective is that integrative studies, including neuropsychological, neuroimaging and pharmacogenetic data may contribute to understanding of the precise mechanisms of action of MPH in the human brain and, consequently, help to elucidate the ADHD pathophysiology.

Taken together, the literature overview of factors influencing treatment response suggest that genetic studies should focus more on MPH adverse side effects or on the use of other drugs. New studies should also be designed to have adequate sample sizes and adjustment for several potential confounding factors frequently neglected, such as comorbidity and sociodemographic factors. Besides that, selection of candidate genes needs to consider variability within metabolic pathway and gene–gene, gene–environmental interactions. Unfortunately, none of the reviewed studies on the pharmacogenetics of ADHD explored gene–gene or gene–environment interactions. Finally, as in other psychiatric disorders, the current state of the art in adult ADHD does not support the use of pharmacogenetic tests in routine clinical practice.

Role of the funding source

Funding for this study was provided by following Brazilian funding agencies: CNPq, INCT de Psiquiatria do Desenvolvimento para Crianças e Adolescentes, FAPERGS, PRONEX, FIPE-HCPA and DECIT/SCTIE/MS/PPSUS. The agencies had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Verônica Contini, Diego L. Rovaris and Marcelo M. Victor managed the literature searches, discussed the results and wrote the first draft. Eugenio H. Grevet and Luis A. Rohde provided supervision and offered guidance in the interpretation of the results. Claiton H.D. Bau had a role in overall supervision and final drafting of the report. All authors contributed substantively to the development of the content of this paper and have approved the final manuscript.

Conflict of interest

Dr. Luis Augusto Rohde was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, Novartis and Shire in the last three years (less than U$ 10,000 per year and reflecting less than 5% of his gross income per year). He also received travel awards (air tickets and hotel) to take part of two Child Psychiatric Meetings from Janssen-Cilag and Novartis in 2010. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last three years: Eli-Lilly, Janssen-Cilag, Novartis, and Shire. Other authors declare no conflicts of interest.

Acknowledgments

Thanks are due to the funding sources: CNPq, INCT-INPD, FAPERGS, PRONEX, FIPE-HCPA and DECIT/SCTIE/MS/PPSUS.

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