Published in final edited form as:
Child Adolesc Psychiatr Clin N Am. 2008 April ; 17(2): 475–xii.

The Pharmacogenomic Era: Promise for Personalizing ADHD Therapy

Mark A. Stein, Ph.D.[a,b] and **James J. McGough, M.D.**[c,d]

a *Professor, Department of Psychiatry, University of Illinois at Chicago*

b*Director of HALP Clinic and ADHD Research Center, University of Illinois at Chicago, Chicago, Illinois*

c*Professor of Clinical Psychiatry, Division of Child and Adolescent Psychiatry, UCLA Semel Institute for Neuroscience and Human Behavior, Los Angeles, California*

d*Director, UCLA Child and Adolescent Psychopharmacology Program and ADHD Clinic, Los Angeles, California*

Synopsis

Currently, ADHD treatment is often determined empirically through trial and error until an adequate response is obtained or side effects occur. ADHD is highly heritable and there is wide individual variability in response to ADHD medications, suggesting that the mechanism of action of stimulant medications may provide clues for genetic predictors of response. The promise of ADHD pharmacogenetics is far reaching, and includes the potential to develop individualized medication regimens that improve symptom response, decrease risk for side effects, improve long-term tolerability, and thus contribute to long-term treatment compliance and improved general effectiveness. Early ADHD pharmacogenetic studies have focused predominantly on catecholamine pathway genes and response to methylphenidate. Future efforts will also examine a wider range of stimulant and non-stimulant medications on a range of outcome measures and time periods. Based upon these studies, the potential for personalizing ADHD treatment in clinical practice will be determined.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common and treatable behavioral syndrome that typically emerges during childhood or adolescence and often persists into adulthood. There are an increasing number of stimulant and non-stimulant medication options for ADHD, with numerous new compounds in development [1]. In acute treatment studies, stimulant medications generally demonstrate large effect sizes on ADHD symptom reduction relative to placebo, with slightly smaller effect sizes in adult studies [2]. Surprisingly, only a minority of children and adolescents with ADHD remain on medication consistently [3],

[a]Corresponding author for proofs and reprints: Mark A. Stein, Ph.D., 1747 W. Roosevelt Road, Rm 155, Chicago, IL 60008, (312) 996-5797 (847) 412-0910 (fax) mstein@uic.edu (email), [c]Coauthor address: James J. McGough, M.D., 300 UCLA Medical Plaza, Suite 1414, Los Angeles, CA 90095, (310) 794-7841 (310) 267-0378 (fax) jmcgough@mednet.ucla.edu (email).

Financial Disclosures
Dr. Stein has received research support from McNeil, Novartis, Eli Lilly Corporation, Shire Pharamceuticals, Cortex Pharmaceuticals, and Phizer Phamaceuticals and serves as a consultant for Novartis Pharamceuticals. Dr. McGough has received research support from and serves as a consultant to Eli Lilly Corporation, Janssen Pharmaceuticals, Novartis Pharmaceuticals, and Shire Pharmaceuticals.

despite persistence of symptoms and impairments. Even among responders, there is marked variability in optimal dosage, duration of effect, and tolerability. Moreover, in spite of acute symptom reduction from ADHD medications, as yet there is little evidence of long-term response and improvement in functioning among those children who received treatment [4, 5]. Furthermore, there are few reliable predictors of medication response. In the absence of these data, treatment is often determined "empirically" in clinical practice through a gradual titration of different dosages and trial and error approach to different medications.

ADHD is a highly heritable disorder [6]. The search for candidate genes associated with ADHD has been largely driven by the understanding that medications for the disorder have drug targets in the catecholamine system [7]. Conversely, it is likely that variability in individual drug response might be related to genetic factors. Spurred by completion of the human genome project [8] there is considerable interest in the translation of molecular genetics research into meaningful clinical applications. Emerging findings in ADHD pharmacogenetics and pharmacogenomics underlie attempts to apply molecular genetics findings to optimize individual patient therapies. Two prior reviews summarized findings in ADHD pharmacogenetics [9,10]. This chapter will review definitions, summarize and update research advances, make recommendations for future investigations, and discuss the potential clinical implications of pharmacogenetics and pharmacogenomics in the management of ADHD.

Pharmacogenetics and Pharmacogenomics

Pharmacogenetics is the study of genetic variability in medication response [11]. Pharmacogenetics encompasses how genetic variation influences both pharmacokinetics, particularly drug metabolism, and pharmacodynamics, in terms of symptom response and side effect profiles. Pharmacogenetics had its l beginnings in the 1950's when clinicians noted increased patterns of adverse reactions within certain families and ethnic groups. In contrast to pharmacogenetics, *pharmacogenomics* is a more recent term, which broadly encompasses efforts to utilize the human genome to better understand and develop pharmacological treatments [12]. Pharmacogenomics refers more specifically to the study of variations in genes and gene products and their relationship to medication response [13]. Based on advances in molecular biology, such as the advent of economical, high throughput gene sequencing and genotyping, and the mapping of the human genome, pharmacogenetic and pharmacogenomic studies have the potential to inform individualized treatment decisions in medicine, and subsequently improve long-term patient outcomes [14]. The promise of ADHD pharmacogenetics is far reaching, and includes the potential to develop individualized medication regimens that improve symptom response, decrease risk for side effects, improve long-term tolerability, and thus contribute to long-term treatment compliance and improved general effectiveness.

Obvious candidates for pharmacogenomic investigations include polymorphic drug-metabolizing enzymes, drug transporters, and targets that affect disease and drug-related pathways [15]. The dramatic and rapid effects of stimulant medications in the management of ADHD symptoms suggests several strong candidates for pharmacogenetic analysis. Numerous candidate gene studies have examined the relationships between polymorphisms in the dopaminergic system and ADHD susceptibility, although only a small percentage of the variance in ADHD susceptibility can be attributed to any one gene [7]. Genome-wide linkage and association studies, including haplotype mapping, also have potential relevance to ADHD pharmacogenomics [16]. With increased identification of single nucleotide polymorphisms (SNP's), SNP tagging of common haplotypes can be economically used to identify regions of interest which better represent common genetic variation in association studies with drug response [17].

Candidate genes associated with increased risk for ADHD based on pooled odds ratios across three or more studies are the dopamine receptors (DRD4 and DRD5), dopamine transporter (DAT1), dopa-β-hydroxylase (DBH), serotonin receptor (HTR1B), serotonin transporter (5-HTT), and synaptosomal-associated protein (SNAP-25) [7]. Other genes of potential interest in pharmacogenetic studies of ADHD include catehol-O-methyltransferase, (COMT), and the adrenergic α2-receptor (ADRA2A). In each of these genes, deep resequencing and association analysis has not been reported to date.

Pharmacogenetic Research Studies

While knowledge about the presumed mechanisms of action of ADHD medications initially informed searches for polymorphisms related to increased risk for the *disorder*, these same polymorphisms are logical candidates to predict *medication outcomes* [9]. Several preliminary studies suggest that candidate genes involved in catecholamine pathways, i.e. genes related to dopamine or norepinephrine, influence individual patient responses to ADHD treatments (Table 1). However, results from several of these reports are contradictory and the nature, magnitude, and direction of purported genetic effects remain unclear. Moreover, the majority of studies have examined predictors of response to methylphenidate, and little attention has been given to other agents. Nonetheless, this seminal research suggests that genetic variability does contribute to treatment response variability in individual patients and provides a foundation for definitive investigations in larger trials.

Dopamine Transporter (DAT1)(SL26A3)

Several reasons support the choice of DAT1 as a candidate gene for ADHD treatment response. An association between ADHD and the 10-repeat (480-base-pair) allele of a variable number tandem repeat (VNTR) in the 3′-untranslated region (3′-UTR) of DAT1 was initially described in 1995 [18]. and replicated in multiple, but not all, follow-up reports [7]. Methylphenidate, and to some extent amphetamine, specifically targets and blocks the dopamine transporter [19,20]. Numerous neuroimaging studies reveal that ADHD patients express increased dopamine transporter densities in striatal regions [22], and that individuals with the 10-repeat allele exhibit approximately 50% greater densities than other genotypes [23]. This suggests that ADHD medications which block the dopamine transporter densities might serve to attenuate the effects of underlying brain pathophysiology. Similarly, functional polymorphisms in DAT1 might influence response to ADHD medications.

The first pharmacogenetic study of ADHD examining the ability of catecholamine related genes to predict response to methylphenidate [24]. This report found a significant difference in response rate among 30 stimulant naïve, African-American youth based on DAT1 genotype. Specifically, 86% of nonresponders were homozygous for the 10-repeat allele compared with 31% of responders (N = 16, 31%) ($\chi^2_{(1)} = 6.9$, p=.008). Two subsequent studies reported a similar relationship between DAT1 genotypes genotype and symptom response. The first examined symptom reductions in 50 European-Brazilian males with ADHD after open titration with methylphenidate up to .7mg/kg/day [24]. Response was defined as ≥ 50% reduction in baseline ADHD ratings, and individuals who failed to meet this threshold were more likely to be homozygous for the 10-repeat allele (Fisher's exact test; one tailed p=.04). A second study that assessed dopamine transporter binding in addition to ADHD symptom reduction in 11 Korean subjects found that only 27% of subjects homozygous for the 10-repeat allele met response criteria compared with 100% of subjects without this genotype ($\chi^2_{(1)}=5.2$, p=.06) [25].

In contrast to the above, one retrospective and three prospective, placebo controlled studies reported improved response to methylphenidate in ADHD youth who were homozygous or heterozygous for the 10-repeat polymorphism. One analysis based on parental retrospective

report in 119 Irish children found that individuals with one or two copies of the 10-repeat allele were more likely to have improved, and a linear relationship existed between the number of 10-repeats and degree of improvement [26]. Similarly, the presence of one or two 10-repeat alleles was associated with higher rates of symptom reduction and reduced impairment in 47 children and adolescents treated with 18 mg., 36mg. and 54mg of OROS methylphenidate [27]. Individuals homozygous for the less common 9-repeat allele demonstrated a non-linear dose-response curve, had more stimulant related side effects, and remained more impaired during treatment

Similar findings were reported for the 9/9 genotype group in a double-blind, placebo controlled trial of 159 children with ADHD conducted in Montreal [28]. Although children with either the 9/10 and 10/10 genotypes displayed a significant positive response to 10 mg. of MPH, the 9/9 genotype group displayed a negative response on parent symptom ratings only (effect size = −. 43. Interestingly, the effect of DAT1 genotype on response was not found on teacher ratings.

In one of the few studies not conducted with methylphenidate. Lott et al [29] reported that college student volunteers with the 9/9 were less able to “feel” amphetamine effects relative to other genotype groups. It should be noted that this was not an ADHD sample, and consisted of college student volunteers. These recent studies suggest a differential effect of stimulants on individuals homozygous for the 9-repeat relative to genotypes containing the 10-repeat.

However, several uncontrolled studies found no association between DAT1 and methylphenidate response, including a sample of 82 Dutch children treated prospectively with < .6 mg/kg/day [30], and a retrospective analysis of 186 youth with ADHD (dose not specified) in the United Kingdom [31]. In addition, an attempt to replicate previous findings in Brazilian youth [25] examined response rates during open label treatment in 111 subjects detected no association between DAT1 genotype and outcomes [32].

In a study of 81 preschoolers with ADHD treated with methylphenidate, there were no genotype effects of DAT1 on a composite measure based on parent and teacher symptom ratings [33}, However, on parent ratings of ADHD symptoms, there was negative effect size (−. 58) for the homozygous 9 repeat genotype. Of note, the difference between parent and teacher ratings iand pharmacogenetic effects of DAT1 is similar to that reported by Joober et al [28].

Recently, the first pharmacogenetic study of adults with ADHD reported no relationship between DAT1 genotype and response in 66 subjects titrated to a maximum methylphenidate dose of 1.3mg/kg/day [34]. However, the sample included only 3 individuals with the 9/9 genotype, and llmited statistical power to detect an effect for this genotype group.

Dopamine Receptor (DRD4)

The dopamine receptor DRD4 is a presumed target of post-synaptic catecholaminergic activity and a likely candidate for predicting variability in medication response. The association of the 7-repeat (48-base-pair) VNTR polymorphism in the coding region of DRD4 with ADHD is one of the most replicated findings in psychiatric genetics, yielding odds ratios ranging from 1.4 to 1.9 [7]. *In vitro* studies further indicate that the 7-repeat allelic variant is functionally less responsive to dopamine [35,36]. Consistent with this idea, one study demonstrated in 45 subjects that patients with at least one copy of the 7-repeat allele required higher doses of methylphenidate for optimal symptom reduction [37]. Conversely, in a separate report on 83 Korean children, subjects who were homozygous for the 4-repeat polymorphism were much more likely to exhibit positive responses on parent and teacher behavioral ratings than those with other genotypes [38]. Other studies have found no relationship between DRD4 genotype and ADHD symptom change [24,30,32,33].

The Preschool ADHD Treatment Study (PATS) was notable in that it focused not only on symptom reduction, but also examined the potential role of genotype in predicting side effects [33]. PATS participants homozygous for the 4-repeat allele were three times more likely to develop abnormal picking behaviors with methylphenidate treatment, while those with one or two copies of the 7-repeat allele were more four times more likely to exhibit social withdrawal with increasing dose. A second study found no associate between genotype and side effects, particularly appetite loss and sleep difficulties [31].

One of the few studies to examine pharmacogenetic predictors of response to ADHD treatments other than methylphenidate found that children with at least one copy of the DRD4 4-repeat allele showed a trend towards improved response on atomoxetine [39]. Response to methylphenidate, in contrast, was unrelated to DRD4 genotype. Furthermore, improvement on the hyperactivity subscale of the ADHD Rating Scale was maximized with the absence of any 7-repeat variant.

Synaptosomal- Associated Protein (SNAP 25)

A relatively unstudied gene with potential effects on ADHD medication response is Synaptosomal -Associated Protein (SNAP25), a neuron-specific protein implicated in exocytotic catecholamine release. Several studies of SNAP25 have revealed small, but significant, increased ADHD risk associated with two single nucleotide polymorphisms (SNPs) (T1069C and T1065G) separated by four base pairs at the 3′ end of the gene [7]. In the *coloboma* mouse, chromosome deletion of SNAP25 gives rise to hyperactive symptoms that are relieved by amphetamine, but not methylphenidate [40]. This is consistent with presumed differences in the mechanisms of action for these compounds, in which amphetamine, but not methylphenidate compensates for reduced exocytotic catecholamine release by reversing the catecholamine diffusion gradient across the transporter.

In methylphenidate treated preschool children with ADHD, individuals homozygous for the T allele at 1065 demonstrated moderately increased improvements, while those who were homozygous for T at 1069 exhibited poorer medication response [32]. More interestingly, children who were homozygous for the less common G allele at 1065 were two to three times more likely to develop sleep difficulties and irritability than those with at least one copy of the T allele. Additionally, those who were homozygous for the less common C allele at 1069 were two to four times more likely to develop tics and other abnormal movements.

Norepinephrine Transporter Protein 1 (NET) and Adrenergic α2A Receptor (ADRA2A)

In addition to their effects on the dopamine system, stimulants also block reuptake at norephinephrine transporters and indirectly act to increase norepinephrine concentrations at adrenergic alpha receptors. Genes for the norepinephrine transporter (NET) and adrenergic alpha 2A receptor (ADRA2A) are therefore also likely candidates to assess genetic contributions to variability in ADHD treatment response. Although not confirmed in meta-analysis, polymorphisms at two SNPs in NET have been associated with ADHD [41]. An association between ADRA2A and ADHD has also been previously demonstrated [42]. Norepinephrine transporter blockade is also the presumed mechanism of activity for the non-stimulant ADHD medication, atomoxetine [43].

One study evaluated the relationship between the G1278A polymorphism at NET and methylphenidate in 45 Han Chinese youth with ADHD and found that individuals homozygous for the less common A/A genotype had decreased symptom reductions compared with the G/A or AA groups [44]. The authors noted, since the G1278A allele has no known functional activity, that the allele might be in linkage disequilibrium with another allele responsible for outcome differences.

Potential effects for polymorphisms at the noradrenergic receptor ADRA2A were assessed in 104 children and adolescents after one and three months of methylphenidate treatment [45]. Following *post hoc* secondary analyses, the investigators reported an interaction between the C1291G polymorphism and improvement over time that explained 30% of the variance in the inattentive score of the Swanson, Nolan, and Pelham (SNAP-IV) Rating Scale. Subjects with at least one copy of the less common G allele showed improved responses in the inattentive domain ($F_{1,104}$=8.5; p<.004). There was no effect on overall SNAP-IV ratings or Hyperactive-Impulsive scores, nor any direct effect of genotype on response.

Metabolic Pathways and Pharmacokinetics

ADHD pharmacogenetic studies have principally examined the potential effects of genetic variability on drug targets, i.e. transporters and receptors [9,10]. Little attention has been devoted to the potential effects of genetic variability on drug metabolism and pharmacokinetics, although these lines of inquiry frequently provide the basis for pharmacogenetic investigations [14]. This might be due to the fact that while methylphenidate is specific in terms of its site of action, its metabolic pathways are poorly understood. It is believed that d,l-methylphenidate undergoes esterification in the blood stream via enzymatic activity of carboxylesterase to d/l ritalinic acid and l-ethylphenidate. One recent report demonstrated inhibition of this metabolic pathway with alcohol ingestion, and also identified one subject as a methylphenidate poor-metabolizer associated with a polymorphism at the carboxylesterase-1 gene [46]. Further study and replication are required to see if this finding underlies the pharmacokinetic variability of methylphenidate generally seen in clinical practice.

Unlike the metabolic products of methylphenidate which are renally excreted, amphetamine undergoes metabolism via hepatic cytochrome P450 (CYP) isozymes. In mammals, amphetamine is metabolized along two major pathways which are differentially employed by various species [47]. In the first pathway, hydroxylation of amphetamine via CYP2D6 yields *p*-hydroxy-amphetamine. Many psychotropic medications are metabolized by CYP 2D6, although it is believed to play a minor role for amphetamine [48]. However, up to 20% of Caucasians and varying percentages of other racial groups are poor metabolizers due to polymorphisms at CYP 2D6, which can have implications for individual patients [49]. In the second pathway, amphetamine undergoes deamination via CYP 3A4 to l-phenylpropane2-one which is subsequently excreted as inactive benzoic acid. The CYP 3A4 amphetamine pathway is dominant in humans.

In a study of an extended release preparation of mixed amphetamine salts, mean drug plasma concentrations following acute dosing were 25% higher in African American children [50]. Previous studies have noted ethnic differences in CYP 3A4-mediated drug metabolism, with Caucasian subjects demonstrating the highest levels of activity [52]. One allelic variant is heterozygous in 64% of African Americans and has been shown to have decreased metabolic activity [52]. Although racial differences in amphetamine pharmacokinetics have not been otherwise examined, and while a definitive association between amphetamine metabolism and polymorphisms at CYP 3A4 has not been demonstrated, these finding represent a unique lead for further examination of the potential role of genetic variability in explaining the pharmacokinetic variability of amphetamines used to treat ADHD.

Atomoxetine, a currently approved nonstimulant medication for ADHD, is metabolized by the CYP2D6 isozyme system. Drug development trials for atomoxetine were notable in that consideration of subjects' CYP2D6 status influenced dosing titration algorithms and subsequently derived approved dosing limits. A recent meta-analysis pooled outcome data from several atomoxetine clinical trials [53]. Poor metabolizers displayed greater symptom improvement than extensive metabolizers, most likely due to higher plasma drug concentration

levels, and were more likely to remain in therapy. Higher rates of appetite decrease and insomnia were reported more frequently in poor metabolizers, who also exhibited greater increases in medication-related pulse and blood pressure changes.

Genome-Wide Investigations

Candidate gene studies presume some knowledge of the biological system under investigation, and require specific hypotheses regarding putative effects of particular polymorphisms. In contrast, genome-wide investigations require no *a priori* hypotheses related to specific genes, but scan the entire genome in an attempt to identify areas harboring genes that contribute some effect on outcome. Several genome-wide scans have identified regions linked with ADHD risk [7,54], including fine mapping by one group to DAT1(55). Genome-wide approaches also have potential utility in pharmacogenetic investigations. One study employed quantitative trait analysis in a genome-wide scan to assess for linkage with methylphenidate response [56]. A linkage peak of moderate significance was identified on chromosome 7, with additional peaks on chromosomes 3, 5, and 9. Further study, including genome-wide association with high density SNP chips, will be necessary to identify the specific genes that influence medication response.

Research Challenges

Preliminary evidence suggests that genetic variability plays some role in predicting treatment response, but that results differ depending on whether parents or teachers are informants. Current studies are also constrained by the type of outcome measures used. Many studies rely on simple dichotomous outcomes, such as responder versus non-responder, which have limited power to detect effects compared with analyses of quantitative measures. Correlations between multiple outcome measures in the same subjects are also known to be fairly weak, raising the question as to which outcome measure best defines positive response [57]. Future pharmacogenetic studies would benefit from consensus on the optimal measures to assess outcome. It remains uncertain, particularly in regards to symptom reduction, the relative contributions of direct genetic effects and effects resulting from medication dose and formulation, as well as individual patient variables including diet and gut motility.

Another contributor to differences in study findings is that pharmacogenetic effects may be different in different ethnic groups. This implies the variants being studies may only be in linkage disequilibrium with other variants.

The majority of ADHD pharmacogenetic studies published to date have examined response to methylphenidate. While this is an obvious choice given the known pathophysiology of DAT1, its association with ADHD, and its serving as a specific target for stimulant action, results from preliminary reports have been inconsistent and contradictory. Some of these discrepant findings might be due to methodological issues, as more consistent findings appear to be emerging from placebo controlled, prospective studies. In addition to small sample sizes, other limitations of most existing trials include open-label or retrospective assessment and medication doses that are not specified or considerably lower than used in community practice for optimal benefit [9]. Since the effects of methylphenidate on ADHD symptoms often follow a linear dose response curve [27], these lower doses might bias against finding significant treatment effects when a less robust dose is utilized.

A critical methodological issue that remains unaddressed is the proper approach to defining genotypes for analysis. In order to minimize the potential for spurious findings and increased Type I errors, investigators must limit their analyses to minimal genotype combinations. For some genes, the risk polymorphisms for ADHD are the less common variants (eg. the 7-repeat allele of DRD4), while for other genes, such as DAT1, it is the more common variant that is

associated with the disorder. For DAT1, the 10/10 and 10/9 genotypes are most common. Notably, earlier studies of DAT1 combined these two common genotypes, which assumed a dominant effect of either the 9 or 10 allele, but failed to test for a recessive effect of the 9/9 genotype. Alternative grouping of genotypes based on the presence of one or more 9 allele has led to different results. Future candidate gene studies would benefit from consensus on optimal strategies to define genotype groupings. Most importantly, without previous evidence of dominance of one allele, genotypes should not be lumped together. Statistical power is a combination of sample size and effect size. Dominance (or lack thereof), may differ between association with etiology of disorder and response to treatment.

At a recent meeting of the ADHD Molecular Genetics Network in Brussels, Belgium, the Pharmacogenetics Working Group proposed several principals to promote research in future ADHD pharmacogenetic studies. These include:

1. Pharmacogenetic studies of ADHD should be methodologically rigorous in terms of the pharmacological intervention, which means the trial should meet criteria for being published on its own. Typically, this means that there should be random assignment to treatment and a placebo or other control group, and preferably random assignment.
2. Response should be measured several ways and at different time points. Secondary functional outcomes and adverse events should be evaluated as well as symptom ratings.
3. Different doses or optimal dose should be evaluated, recognizing that dose ranging and forced titration designs will more likely elicit pharmacogenetics effects than flexible dosing.
4. Multiple genes should be examined
5. Genotyping quality control must be performed, ideally including cross-laboratory and cross-method reliability checks
6. Samples large enough to look at gene by environment interactions should be obtained.
7. Trials sponsored by pharmaceutical companies should routinely collect DNA for pharmacogenetic and subgroup analysis.

Clinical Applications

Stimulant medications are acknowledged as first-line treatments for ADHD [58], although the evidence supporting sustained benefit from pharmacotherapy remains less clear [59]. One 5-year prospective study demonstrated that over half of the participants failed to continue medication into the second treatment year, and many of those who did continue therapy reported clinically significant side effects [60]. The authors concluded that side effects and perceived tolerability were major factors in the decision by patients to discontinue treatment. Open-label follow-up studies of clinical trials subjects taking either methylphenidate or amphetamine showed that fewer than 60% of previously stabilized patients remained on medication after 12 months of treatment, although those who remained in therapy showed sustained improvements from baseline [61,62]. It is therefore clear, that in spite of the overall effectiveness of stimulant medications in the short-term relief of ADHD symptoms, there are considerable impediments to remaining on long-term treatment.

Although most published ADHD pharmacogenetic studies have emphasized genetic predictors of symptom improvement, a more practical clinical application might lie in prediction of side effect risk and medication tolerability. Side effects are major impediments to long term treatment adherence. In the Preschool ADHD Treatment Study, development of irritability and increased emotionality were two major reasons subjects discontinued medication therapy

[63]. Interestingly, pharmacogenetic analyses from that trial revealed genetic predictors of irritability, social withdrawal, and abnormal movements [33]. Conceivably, an awareness of increased side effect risk could guide clinicians towards treatment choices that are more likely to be tolerated over time with less patient exposure to medications that are unlikely to provide benefit.

The most promising clinical application of ADHD pharmacogenetics and pharmacogenomics might lie in the development of novel ADHD treatments. The identification of genes that increase susceptibility for ADHD or predict ADHD treatment response might promote the discovery of new drug targets for future pharmaceutical development. It should also be possible, as the cost of genotyping individual patients decreases, to enroll subsets of patients into clinical trials who are more likely to exhibit positive responses and less likely to suffer untoward effects. Ultimately, it is hoped that this type of research will allow clinicians to tailor individual treatment choices based on genotype.

Summary

Not surprisingly, pharmacogenetics and pharmacogenomics research efforts in children, adolescents, and adults are expanding world-wide. To date, several promising findings related to diminished response and specific side effects have been reported. Future efforts will also examine a wider range of stimulant and non-stimulant medications on a range of outcome measures and time periods. It is hoped that eventually ADHD treatment outcomes will be improved by a more personalized approach to determining treatments. Potentially, this could result in better understanding of treatment failures and the development of more targeted ADHD treatments. Although research on positive and negative predictive value is necessary prior to attempts to apply preliminary findings to contemporary practice, such studies are currently ongoing. If successful, personalized ADHD therapy will move quickly from the “promise” to the “practical” phase.

Acknowledgements

This work was supported by Grant No. MH70564 (to Dr. Stein) from the National Institute of Mental Health. The authors would like to thank Edwin H. Cook Jr. M.D. for his thoughtful review and helpful comments.

References

1. Prince J. Pharmacotherapy of attention-deficit hyperactivity in children and adolescents: update on new stimulant preparations, atomoxetine, and novel treatments. Child Adolesc Psychiatr Clin N Am 2006;15:15–30.
2. Faraone SV, Biederman J, Spencer TJ, Aleardi M. Comparing the efficacy of medications for ADHD using meta-analysis. MedGenMed 2006;8:4. [PubMed: 17415287]
3. Charach A, Ickowicz A, Schachar R. Stimulant treatment over five years; adherence, effectiveness, and adverse events. J Am Acad Child Adolesc Psychiatry 2004;43:559–567. [PubMed: 15100562]
4. Schachar RJ, Tannock R. Childhood hyperactivity and psychostimulants: a review of extended treatment studies. J Child Adolesc Psychopharmacol 1993;3:81–97.
5. MTA Cooperative Group. National Institute of Mental Health Multimodal Treatment Study of ADHD follow-up: 24-month outcomes of treatment strategies for attention-deficit/hyperactivity disorder. Pediatrics 2004;113:754–761. [PubMed: 15060224]
6. Faraone SV, Doyle AE. The nature and heritability of attention-deficit/hyperactivity disorder. Child Adolesc Psychiatr Clin N Am 2001;10:299–316. [PubMed: 11351800]
7. Faraone SV, Perlis R, Doyle AE, Smoller JW, Goralnick JJ, Homgren MA, et al. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57:1313–1323. [PubMed: 15950004]
8. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al. Initial sequencing and analysis of the human genome. Nature 2001;409:860–861. [PubMed: 11237011]

9. McGough JJ. Attention-deficit/hyperactivity disorder pharmacogenomics. Biol Psychiatry 2005;57:1367–1373. [PubMed: 15950009]
10. Polanczyk G, Zeni C, Genro J, Roman T, Hutz MH, Rohde LA. Attention-deficit/hyperactivity disorder: advancing on pharmacogenomics. Pharmacogenomics 2005;6:225–234. [PubMed: 16013954]
11. Weber, WW. Pharmacogenetics. New York: Oxford Press; 1997.
12. Aitchison, KJ.; Gill, M. Pharmacogenetics in the postgenomic era. In: Eeds, R.; Plomin, J.; Devries, I.; Craig, P., editors. Behavioral Genetics in the Postgenomic Era McGuffin. Washington, DC: American Psychological Association; 2003. p. 335-361.
13. Meyer UA. Pharmacogenetics and adverse drug reactions. Lancet 2000;356:1667–1671. [PubMed: 11089838]
14. Staddon S, Aranz MJ, Mancama D, Mata I, Kerwin RW. Clinical applications of pharmacogenetics in psychiatry. Psychopharmacology 2002;162:18–23. [PubMed: 12107612]
15. Masellis M, Basile V, Muglia P, Ozdemir V, Macciardi FM, Kennedy JL. Psychiatric pharmacogenetics: Personalizing psychostimulant therapy in attention-deficit/hyperactivity disorder. Behav Brain Res 2002;130:85–90. [PubMed: 11864722]
16. Sklar P. Principles of haplotype mapping and potential applicatons to attention-deficit hyperactivity disorder. Biol Psychiatry 2005;57:1357–1366. [PubMed: 15950008]
17. Goldstein DB. Pharmacogenetics in the laboratory and the clinic. N Engl J Med 2003;348:553–556. [PubMed: 12571264]
18. Cook EH, Stein MA, Krasowski MD, Cox NJ, Oikon DM, Kieffer JE. Association of attention-deficit disorder and the dopamine transporter gene. Am J Hum Genet 1995;56:993–998. [PubMed: 7717410]
19. Melega WP, Williams AC, Schmitz DA, DiStefano EW, Cho AK. Pharmacokinetic and pharmacodynamic analysis of the actions of d-amphetamine and d-methamphetamine on the dopamine terminal. J Pharmacol Exp Ther 1995;274:90–96. [PubMed: 7616454]
20. Volkow ND, Wang G, Fowler JS, Telang F, Maynard L, Logan J, et al. Evidence that methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. Am J Psychiatry 2004;161:1173–1180. [PubMed: 15229048]
21. Spencer TJ, Biederman J, Madras BK, Faraone SV, Dougherty DD, Bonab AA, et al. In vivo neuroreceptor imaging in attention-deficit/hyperactivity disorder: a focus on the dopamine transporter. Biol Psychiatry 2005;57:1293–1300. [PubMed: 15950001]
22. VanNess SH, Owens MJ, Kilts CD. The variable number of tandem repeats element in DAT1 regulates in vitro dopamine transporter density. BMC Genet 2005;6:55. [PubMed: 16309561]
23. Winsberg BG, Comings DE. Association of the dopamine transporter gene (DAT1) with poor methylphenidate response. J Am Acad Child Adoelsc Psychiatry 1999;38:1474–1477.
24. Roman T, Szobot C, Martine S, Biederman J, Rohde LA, Hutz MH. Dopamine transporter gene and response to methylphenidate in attention-deficit/hyperactivity disorder. Pharmacogenetics 2002;12:497–499. [PubMed: 12172219]
25. Cheon KA, Ryu YH, Kim JW, Cho DY. The homozygosity for the 10-repeat allele at dopamine transporter gene and dopamine transporter density in Korean children with attention deficit hyperactivity disorder: relating to treatment response to methylphenidate. Eur Neuropsychopharmacol 2005;15:95–101. [PubMed: 15572278]
26. Kirley A, Lowe N, Hawi A, Mullins C, Daly G, Waldman I, et al. Association of the 480 bp DAT1 allele with methylphenidate response in a sample of Irish children with ADHD. Am J Med Genetics 2003;121B:50–54.
27. Stein MA, Waldman ID, Sarampote CS, Seymour KE, Robb AS, Conlon C, et al. Dopamine transporter genotype and methylphenidate dose response in children with ADHD. Neuropsychopharmacology 2005;30:1374–1382. [PubMed: 15827573]
28. Joober R, Grizenko Sengupta SN, Ben Amor L, Schwartz G, Karama S, et al. Dopamine transporter 3′-UTR VNTR genotype and ADHD: A pharmaco-behavioral genetic study with methylphenidate. Neuropsychopharmacology 2006;32:1370–1376. [PubMed: 17063150]
29. Lott D, Kim S, Cook E, deWItt H. Dopamine transporter genotype and amphetamine response. Neuropsychopharmacology 2003;30:602–609. [PubMed: 15602501]

30. Van der Meulen EM, Bakker SC, Pauls DL, Oteman N, Kruitwagen CL, Pearson PL, et al. High sibling correlation on methylphenidate response but no association with DAT1-10R and DRD4–7 alleles in Dutch sibpairs with ADHD. J Child Psychol Psychiatry 2005;46:1074–1080. [PubMed: 16178931]
31. Langley K, Turic D, Peirce TR, Mills S, Van Den Bree MB, Owen MJ, et al. No support for association between the dopamine transporter (DAT1) gene and ADHD. Am J Med Genet B Neuropsychiatr Genet 2005;139B:7–10. [PubMed: 16082688]
32. Zeni CP, Guimarães AP, Polanczyk GV, Genro JP, Roman T, Hutz MH, et al. No significant association between response to methylphenidate and genes of the dopaminergic serotonergic systems in a sample of Brazilian children with attention-deficit/hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 2007;144:391–394. [PubMed: 17171656]
33. McGough JJ, McCracken JT, Swanson J, Riddle M, Kollins SH, Greenhill LL, et al. Pharmacogenetics of methylphenidate response in preschoolers with ADHD. J Am Acad Child Adolesc Psychiatry 2006;45:1314–1322. [PubMed: 17023870]
34. Mick E, Biederman J, Spencer T, Faraone SV, Sklar P. Absence of association with DAT1 polymorphism and response to methylphenidate in a sample of adults with ADHD. Am J Med Genet 2006;141:890–894.
35. Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. J Neurochem 1995;65:1157–1165. [PubMed: 7643093]
36. Van Tol HH, Wu CM, Guan HC, Ohara K, Bunzow JR, Civelli O, et al. Multiple dopamine D4 receptor variants in the human population. Nature 1992;358:149–152. [PubMed: 1319557]
37. Hamarman S, Fossella J, Ulger C, Brimacombe M, Dermody J. Dopamine receptor 4 (DRD4) 7-repeat allele predicts methylphenidate dose response in children with attention deficit hyperactivity disorder. J Child Adolesc Psychopharmacology 2004;14:564–574.
38. Cheon K, Kim B, Cho S. Association of 4-repeat allele of the dopamine D4 receptor gene III polymorphism and response to methylphenidate treatment in Korean ADHD children. Neuropsychopharamcology 2007;32:1377–1383.
39. Sallee, F.; Newcorn, JA.; Allen, AJ.; Stein, MA.; McDougle, C.; Sethuraman, S. Pharmacogenetics of atomoxetine: relevance of DRD4. Scientific Proceedings of the 51th Annual Meeting of the American Academy of Child and Adolescent Psychiatry; Washington, DC. October 2004;
40. Wilson MC. Coloboma mouse mutant as an animal model of hyperkinesis and attention deficit hyperactivity disorder. Neurosic Biobeh Rev 2000;24:51–57.
41. Bobb AJU, Addington AM, Sidransky E, Gornick MC, Lerch JP, Greenstein DK, et al. Support for association between ADHD and two candidate genes: NET1NET and DRD1. Am J Med Genet B Neuropsychiatr Genet 2005;134:67–72. [PubMed: 15717291]
42. Roman T, Schmitz M, Polanczyk GV, Eizirik M, Rohde LA, Hutz MH. Is the α-2A adrenergic receptor gene (*ADRA2A*) associated with attention-deficit/hyperactivity disorder? Am J Med Genet B Neuropsychiatr Genet 2003;120:116–120. [PubMed: 12815749]
43. Michelson D, Faries D, Wernicke J, Kelsey D, Kendrick K, Sallee FR, et al. Atomoxetine in the treatment of children and adolescent with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled, dose-response study. Pediatrics 2001;108:E83. [PubMed: 11694667]
44. Yang L, Wang Y-F, Li J, Faraone SV. Association of norepinephrine transporter gene (NET) with methylphenidate response. J Am Acad Child Adolesc Psychiatry 2004;43:1154–1158. [PubMed: 15322419]
45. Polanczyk G, Zeni C, Genro JP, Guimarães AP, Roman T, Hutz MH, et al. Association of the adrenergic α2A receptor gene with methylphenidate improvement of inattentive symptoms in children and adolescents with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2007;64:218–224. [PubMed: 17283289]
46. Patrick KS, Straughn AB, Minhinnett RR, Yeatts SD, Herrin AE, DeVane CL, et al. Influence of ethanol and gender on methylphenidate pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 2007;81:346–353. [PubMed: 17339864]
47. Dring LG, Smith RL, Williams RT. The metabolic fate of amphetamine in man and other species. Biochem J 1970;116:425–35. [PubMed: 4985156]

48. Markowitz JS, Patrick KS. Pharmacokinetic and pharmacodynamic drug interactions in the treatment of attention-deficit hyperactivity disorder. Clin Pharmacokinet 2001;40:753–72. [PubMed: 11707061]
49. Meyer UA, Zanger UM. Molecular mechanism of genetic polymorphisms of drug metabolism. Annu Rev Toxicol 1997;37:269–296.
50. McGough JJ, Biederman J, Greenhill LL, McCracken JT, Spencer TJ, Posner K, et al. Pharmacokinetics of SLI381 (Adderall XR), and extended-release formulation of Adderall. J Am Acad Child Adolesc Psychiatry 2003;42:684–691. [PubMed: 12921476]
51. Xie H-G, Kim RB, Wood AJJ, Stein CM. Molecular basis of ethnic differences in drug disposition and response. Annu Rev Pharmacol Toxicol 2001;41:815–850. [PubMed: 11264478]
52. Wandel C, Witte JS, Hall JM, Stein CM, Wood AJ, Wilkinson GR. CYP3A activity in African American and European American men; population differences and functional effect of the CYP3A4*1B5′-promoter region polymorphisms. Clin Pharmacol Ther 2000;68:82–91. [PubMed: 10945319]
53. Michelson D, Read HA, Ruff D, Witcher J, Zhang S, McCracken J. CY2D6 and clinical response to atomoxetine in children and adolescents with ADHD. J Am Acad Child Adolesc Psychiatry 2007;46:242–251. [PubMed: 17242628]
54. Waldman ID, Gizer IR. The genetics of attention deficit hyperactivity disorder. Clin Psychol Rev 2006;26:396–432. [PubMed: 16513236]
55. Friedel S, Saar K, Demple A, Walitza S, et al. Association and linkage of allelic variants of the dopamine transporter gene in ADHD. Molecular Psychiatry. in press
56. Van der Meulen, EM.; Bakker, SC.; Pauls, DL.; Sinnke, RJ.; Buitelaar, J. A genome-wide Quantitative Trait Locus analysis on methylphenidate response rate in Dutch sibpairs with attention-deficit/hyperactivity disorder. Scientific Proceedings of the 16th World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions; Berlin, Germany. August 2004;
57. Pelham, WE.; Millich, R. Individual differences in response to Ritalin in class work and social behavior. In: Greenhill, LL.; Osman, B., editors. Ritalin: Theory and Patient Management. New York: Mary Ann Liebert; 1991.
58. Plizska SR, Crismon ML, Hughes CW, Conners CK, Emslie GJ, Jensen PS, et al. The Texas Children's Medication Algorithm Project; revision of the algorithm for pharmacotherapy of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2006;45:642–657. [PubMed: 16721314]
59. Spencer T, Biederman J, Wilens T, Harding M, O'Donnell D, Griffin S. Pharmacotherapy of attention deficit hyperactivity disorder across the lifespan. J Am Acad Child Adolesc Psychiatry 1996;35:409–428. [PubMed: 8919704]
60. Charach A, Ickowicz A, Schachar R. Stimulant treatment over five years; Adherence, effectiveness, and adverse events. J Am Acad Child Adolesc Psychiatry 2004;43:559–567. [PubMed: 15100562]
61. McGough JJ, Biederman J, Wigal S, Lopez FA, McCracken JT, Zhang Y, et al. Long-term tolerability and effectiveness of once-daily mixed amphetamine salts (Adderall XR) in children with ADHD. J Am Acad Child Adolesc Psychiatry 2005;44:530–538. [PubMed: 15908835]
62. Wilens T, Pelham W, Stein M, Conners CK, Abikoff H, Atkins M, et al. ADHD treatment with once-daily OROS methylphenidate: interim 12-month results from a long-term open-label study. J Am Acad Child Adolesc Psychiatry 2003;42:424–433. [PubMed: 12649629]
63. Wigal T, Greenhill L, Chuang S, McGough J, Vitiello B, Skrobala A, et al. Safety and tolerability of methylphenidate in preschool children with ADHD. J Am Acad Child Adolesc Psychiatry 2006;45:1294–1303. [PubMed: 17028508]

Table 1

Pharmacogenetic Studies of Methylphenidate in Attention-Deficit/Hyperactivity Disorder.

Gene	Study	Sample Size	Study Location	Design	Outcome
Dopamine Transporter (DAT1)	Winsberg & Comings 1999	30	New York, USA	Prospective, open-label	Decreased response with homozygous 10-repeat
	Roman et al. 2002	50	Brazil	Prospective, open-label	Decreased response with homozygous 10-repeat
	Kirley et al. 2003	119	Ireland	Retrospective report	Increased response with number of 10-repeat
	Hamarman et al. 2004	45	New York, USA	Prospective, open-label	No effect.
	Cheon et al. 2005	11	Korea	Prospective, open-label with SPECT imaging	Decreased response with homozygous 10-repeat
	Stein et al. 2005	47	Washington, D.C.	Prospective, double-blind, placebo-controlled, dose response	Different dose response curves by DAT1 genotype, decreased response with homozygous 9-repeat
	Joober et al. 2006	159	Montreal, Canada.	Prospective, double-blind, placebo-controlled	Worsening with homozygous 9-repeat on parent ratings
	Van der Meulen et al. 2005	82	Netherlands	Retrospective report	No effect
	Langley et al. 2005	236	Wales, U.K	Retrospective report	No effect
	McGough et al. 2006	81 (preschoolers)	U.S.A. (6 sites)	Prospective, double-blind, placebo controlled	No effect on primary outcome composite measure
	Mick et al., 2006	66 (adults)	Boston,Ma.	Prospective study of MPH arm	No effect
	Zeni et al. 2007	111	Brazil.	Prospective, open-label	No effect
Dopamine Receptor (DRD2)	Winsburg & Comings 1999	30	New York, USA	Prospective, open-label	No effect
Dopamine Receptor (DRD4)	Winsburg & Comings 1999	30	New York, U.S.A.	Prospective, open-label	No effect
	Hamarman et al. 2004	45	New York, U.S.A.	Prospective, open-label	higher doses for rmalization needed for 7- peat..
	McGough et al. 2006	81	U.S.A (6 sites)	Prospective, double-blind, placebo controlled	No effect on symptoms. Increased picking, irritability, social withdrawal.
	Cheon et al., 2007	83	Korea	Prospective, open-label	Decreased response with7-repeat allele
	Zeni et al. 2007	111	Brazil	Prospective, open-label	No effect
Synaptosomal-Associated Protein (SNAP25)	McGough et al. 2006	81	U.S.A (6 sites)	Prospective, double-blind, placebo controlled	Increased irritability and abnormal movements
Norepinephrine Transporter Protein 1 (NET)	Yang et al. 2004	45	China	Prospective, open-label	Decreased response for homozygous A-allele
Adrenergic α2A Receptor (ADRA2A)	Polanczyk et al. 2007	106	Brazil	Prospective, open-label	Improved response on Inattention symptoms with G allele.
Serotonin Receptors (HTR1B, HTR2A)	Zeni et al. 2007	111	Brazil	Prospective, open-label	No effect
Serotonin Transporter (5-HTT)	Zeni et al. 2007	111	Brazil	Prospective, open-label	No effect