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Literature Summary – Genecept Assay 2.0

January, 2016

The following is a summary of the key published literature relevant to a variety of genetic variations. The purpose of this document is to summarize the information available. Individual patients vary and this information is not intended to replace the clinician's responsibilities in clinical decision making.

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Literature Summary

Pharmacodynamic Genes

1.1 Gene Tested: Serotonin Transporter (SLC6A4)

Selective Serotonin Reuptake Inhibitor Pathway, Pharmacodynamics
https://www.pharmgkb.org/pathway/PA161749006 [1]

> "Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that influences multiple processes, including autonomic function, motor activity, hormone secretion, cognition, and complex processes associated with affection, emotion, and reward…The solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (SLC6A4) is responsible for terminating the action of 5-HT in the synaptic cleft. Released serotonin is transported back into the presynaptic terminals via this integral membrane protein…The molecular target for SSRI is SLC6A4, resulting in an inhibition of 5-HT reuptake in the presynapse from the synaptic cleft. " [1]

Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder
http://www.ncbi.nlm.nih.gov/pubmed/18982004 [2]

Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy
http://www.ncbi.nlm.nih.gov/pubmed/22137564 [3]

Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients
http://www.ncbi.nlm.nih.gov/pubmed/17146470 [4]

Polymorphisms in Serotonergic Pathways Influence the Outcome of Antidepressant Therapy in Psychiatric Inpatients
http://www.ncbi.nlm.nih.gov/pubmed/24192302 [5]

SLC6A4 Polymorphisms and Age of Onset in Late-life Depression on Treatment Outcomes with Citalopram: A Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Report
http://www.ncbi.nlm.nih.gov/pubmed/23973251 [6]

Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy
http://www.ncbi.nlm.nih.gov/pubmed/24151799 [7]

> Three comprehensive meta-analyses[2-4] published in the past several years verify that the serotonin transporter polymorphism is strongly related to response to SSRI medications (Odds Ratios (ORs): 1.58, CI = 1.16-2.16, p = 0.004; 2.01, CI = 1.39–2.89, p = 0.0002), as well as remission (ORs: 1.53, C.I. 1.14-2.04, p = 0.004; 1.42, CI = 0.98–2.04, p = 0.06). More recent data also clearly indicate that individuals with the short transporter allele are less likely to respond to SSRIs and less likely to achieve remission. [5-7]

Pharmacogenetics of major depressive disorder: top genes and pathways toward clinical applications
http://www.ncbi.nlm.nih.gov/pubmed/25980509 [8]

> "..cumulative evidence supports the involvement of some genes and molecular pathways in antidepressant efficacy. The best single genes are SLC6A4, HTR2A, BDNF, GNB3, FKBP5, ABCB1, and cytochrome P450 genes (CYP2D6 and CYP2C19). Molecular pathways involved in inflammation and neuroplasticity show the greatest support. The first studies evaluating benefits of genotype-guided antidepressant treatments provided encouraging results and confirmed the relevance of SLC6A4, HTR2A, ABCB1, and cytochrome P450 genes. Further progress in genotyping and data analysis would allow to move forward and complete the understanding of antidepressant pharmacogenetics and its translation into clinical applications." [8]

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Serotonin transporter gene (5-HTTLPR) polymorphism and efficacy of selective serotonin reuptake inhibitors—do we have sufficient evidence for clinical practice

http://www.ncbi.nlm.nih.gov/pubmed/24558768 [9]

> "This paper gives an overview of 35 studies investigating the efficacy of SSRI antidepressants in dependence of 5-HTTLPR polymorphism… Briefly, the great majority of studies conducted have shown that L-allele carriers have a faster and better response to SSRI antidepressants, if they are Caucasians…Pharmacogenetic analysis of 5-HTTLPR polymorphism has proven to be economically cost-effective considering the recurrent course of the disease. It would appear that the response to SSRI antidepressants and the development of adverse reactions are associated with 5-HTTLPR polymorphism in Caucasians and this pharmacogenetic analysis could be one of the first in future clinical practice." [9]

Does pretreatment testing for serotonin transporter polymorphisms lead to earlier effects of drug treatment in patients with major depression? A decision-analytic model

http://www.ncbi.nlm.nih.gov/pubmed/17617292 [10]

> "An estimated 30% to 40% of patients with depression do not sufficiently respond to treatment with selective serotonin reuptake inhibitors (SSRIs) and the period in which treatment efficacy can be assessed is relatively long… A decision-analytic model was used to assess whether pretreatment genetic testing for 5-HTTLPR, a polymorphism of the SLC6A4 genotype, could be an efficient tool in the treatment of depression… The findings of this study suggest that performing genetic testing before prescribing antidepressant treatment may lead to greater numbers of patients experiencing remission early in treatment." [10]

Serotonin transporter 5-HTTLPR genotype moderates the effects of childhood adversity on posttraumatic stress disorder risk: a replication study

http://www.ncbi.nlm.nih.gov/pubmed/22693124 [11]

> "We reported that the 5-HTTLPR polymorphism in the promoter region of the serotonin transporter gene (SLC6A4) moderates the effect of childhood adversity on posttraumatic stress disorder (PTSD) risk [Xie et al. (2009); Arch Gen Psychiatry 66 (11): 1201-1209]. In the present study, we considered 5,178 subjects (a group with generally high substance dependence comorbidity, as for our previous study) using similar methodology to replicate our previous results. We found that, as reported in our previous study, in individuals with childhood adversity, the presence of one or two copies of the S allele of 5-HTTLPR increased the risk to develop PTSD. This gene-environment interaction effect was present in European Americans (EAs), but not in African Americans (AAs; EAs, OR = 1.49, 95% CI = 1.07-2.08, P = 0.019; AAs, OR = 0.90, 95% CI = 0.60-1.35, P = 0.62)." [11]

An examination of the association between 5-HTTLPR, combat exposure, and PTSD diagnosis among U.S. veterans

http://www.ncbi.nlm.nih.gov/pubmed/25793742 [12]

> "Objective was to examine the association between the 5-HTTLPR polymorphism of the serotonin transporter (SLC6A4) gene, combat exposure, and posttraumatic stress disorder (PTSD) diagnosis and among two samples of combat-exposed veterans…The first sample included 550 non-Hispanic Black (NHB) combat-exposed veterans. The second sample included 555 non-Hispanic White (NHW) combat-exposed veterans…Within the NHB sample, a significant additive effect was observed for 5-HTTLPR (OR = 1.502, p = .0025), such that the odds of having a current diagnosis of PTSD increased by 1.502 for each additional S' allele. No evidence for an association between 5-HTTLPR and PTSD was observed in the NHW sample…The present study suggests that there may be an association between 5-HTTLPR genotype and PTSD diagnosis among NHB veterans; however, no evidence for the hypothesized 5-HTTLPR x combat interaction was found. [12]

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1.2 Gene Tested: Calcium Channel, L-type Voltage-gated, Alpha 1C Subunit (CACNA1C)

Functional Implications of a psychiatric risk variant within *CACNA1C* in induced human neurons
http://www.ncbi.nlm.nih.gov/pubmed/25623946 [13]

"Several large-scale genome-wide association studies have revealed a strong association between susceptibility for psychiatric disorders, including bipolar disease, schizophrenia and major depression, and a haplotype located in an intronic region of the L-type voltage-gated calcium channel (VGCC) subunit gene CACNA1C (peak associated SNP rs1006737), making it one of the most replicable and consistent associations in psychiatric genetics. In the current study, we used induced human neurons to reveal a functional phenotype associated with this psychiatric risk variant... These studies demonstrate that the risk genotype at rs1006737 is associated with significant functional alterations in human iNs, and may direct future efforts at developing novel therapeutics for the treatment of psychiatric disease." [13]

Molecular neurobiological clues to the pathogenesis of bipolar disorder
http://www.ncbi.nlm.nih.gov/pubmed/26210959 [14]

"Bipolar disorder is a serious psychiatric disorder, with a high heritability and unknown pathogenesis. Recent genome-wide association studies have identified the first loci, implicating genes such as CACNA1C and ANK3. The genes highlight several pathways, notably calcium signalling, as being of importance. Molecular studies suggest that the risk variants impact on gene regulation and expression." [14]

Identification of pathways for bipolar disorder: a meta-analysis
http://www.ncbi.nlm.nih.gov/pubmed/24718920 [15]

"Among 966 genes, 226 were empirically significant ($P < .05$). Seventeen pathways were overrepresented in analyses of the initial data set. Six of the 17 pathways were associated with BP in both the initial and replication samples: corticotropin-releasing hormone signaling, cardiac β-adrenergic signaling, phospholipase C signaling, glutamate receptor signaling, endothelin 1 signaling, and cardiac hypertrophy signaling. Among the 226 genes, 9 differed in expression in the dorsolateral prefrontal cortex in patients with BP: CACNA1C, DTNA, FOXP1, GNG2, ITPR2, LSAMP, NPAS3, NCOA2, and NTRK3." [15]

Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder
http://www.ncbi.nlm.nih.gov/pubmed/18711365 [16]

CACNA1C (Ca(v)1.2) in the pathophysiology of psychiatric disease
http://www.ncbi.nlm.nih.gov/pubmed/22705413 [17]

Evidence for single nucleotide polymorphisms and their association with bipolar disorder
http://www.ncbi.nlm.nih.gov/pubmed/24143106 [18]

Suggestive evidence for association between L-type voltage-gated calcium channel (CACNA1C) gene haplotypes and bipolar disorder in Latinos: a family-based association study
http://www.ncbi.nlm.nih.gov/pubmed/23437964 [19]

Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4
http://www.ncbi.nlm.nih.gov/pubmed/21926972 [20]

Replication of previous genome-wide association studies of psychiatric diseases in a large schizophrenia case-control sample from Spain
http://www.ncbi.nlm.nih.gov/pubmed/25124521 [21]

Replication of brain function effects of a genome-wide supported psychiatric risk variant in the CACNA1C gene and new multi-locus effects
http://www.ncbi.nlm.nih.gov/pubmed/24642287 [22]

CACNA1C has consistently emerged in association studies with bipolar disorder and schizophrenia. Ca(v)1.2 is involved in the proper function of numerous neurological circuits including those involving the hippocampus, amygdala, and mesolimbic reward system, which are strongly implicated in psychiatric disease pathophysiology. Several large genome-wide association studies (GWAS) have strongly implicated the CACNA1C SNP rs1006737 as a risk variant for bipolar disorder. One study in 4,387 cases and 6,209 controls had a combined p = 7.0 x 10(-8), rs1006737)[16]. The results suggest that ion channelopathies may be involved in the pathogenesis of bipolar disorder. [16-22]

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Genetic analysis of SNPs in CACNA1C and ANK3 gene with schizophrenia: A comprehensive meta-analysis
http://www.ncbi.nlm.nih.gov/pubmed/26227746 [23]

Evaluating the association between CACNA1C rs1006737 and schizophrenia risk: A meta-analysis
http://www.ncbi.nlm.nih.gov/pubmed/25588813 [24]

Many GWAS have been conducted examining the relationship of CACNA1C rs1006737 to bipolar disorder and schizophrenia. Recently, two extensive meta-analyses have reviewed these studies and supported the association of rs1006737 as a risk for schizophrenia in a wide range of ethnicities. One study concluded, "a significant difference was identified between patients and controls for the A-allele of rs1006737 in combined studies (Z = 6.02, P = 1.74E-09), in European studies (Z = 4.08, P = 4.50E-05), and in Asian studies (Z = 4.60, P = 4.22E-06) [23]." The other study demonstrated similar findings, "our results revealed a significant association between rs1006737 and schizophrenia (allelic model, P = 4.39 × 10(-6), pooled odds ratio [OR] = 1.20), and the results were much strengthened when the European and East Asian samples were combined together (P = 2.40 × 10(-17) , pooled OR = 1.12).[24]" [23,24]

What is the impact of genome-wide supported risk variants for schizophrenia and bipolar disorder on brain structure and function? A systematic review.
http://www.ncbi.nlm.nih.gov/pubmed/25858580 [25]

"The powerful genome-wide association studies (GWAS) revealed common mutations that increase susceptibility for schizophrenia (SZ) and bipolar disorder (BD), but the vast majority were not known to be functional or associated with these illnesses. To help fill this gap, their impact on human brain structure and function has been examined. We systematically discuss this output to facilitate its timely integration in the psychosis research field; and encourage reflection for future research." [25]

CACNA1C gene and schizophrenia: a case-control and pharmacogenetic study
http://www.ncbi.nlm.nih.gov/pubmed/26049408 [26]

"In the case-control study, rs1006737 (P=0.05) and rs2239104 (P=0.03) were associated with SCZ. Further, the rs10848635-rs1016388-rs1006737 haplotype was also associated with SCZ (P=0.03, simulate P=0.02)… Our findings further support a role for the CACNA1C gene, particularly for the rs1006737, in SCZ. Further, five SNPs were associated with improvement in PANSS subscales, suggesting a role for this gene in antipsychotic response as well." [26]

The effects of the CACNA1C rs1006737 A/G on affective startle modulation in healthy males
http://www.ncbi.nlm.nih.gov/pubmed/25841664 [27]

"Here we studied the impact of the risk A allele on affective startle modulation….The [results] taken together suggest that healthy homozygous individuals for the risk A allele for major depression and bipolar disorder are sensitive to contextual aversion which leads to a reactivity pattern akin to a mixed anxious/depressed phenotype. This phenotype reflects the non-specific anxiety/ depression psychopathology that often precedes the formal clinical disorders associated with this gene variant…Our findings provide phenotypic detail of the CACNA1C AA genotype in non-symptomatic individuals, which suggest primary effects in emotional circuitry, consistent with previously documented alterations in hippocampal/amygdala processing." [27]

Increased vulnerability of hippocampal neurons with age in culture: Temporal association with increases in NMDA receptor current, NR2A subunit expression and recruitment of L-type calcium channels
http://www.ncbi.nlm.nih.gov/pubmed/17433272 [28]

The results indicate that enhanced excitotoxic vulnerability with age in culture was associated with a substantial increase in NMDA-R current with apparent recruitment of L-VGCCs into the excitotoxic process. [28]

Association of rs1006737 in CACNA1C with alterations in prefrontal activation and fronto-hippocampal connectivity
http://www.ncbi.nlm.nih.gov/pubmed/23404764 [29]

"Genome-wide association studies have identified the rs1006737 single nucleotide polymorphism (SNP) in the CACNA1C gene as a susceptibility locus for schizophrenia and bipolar disorder. The homozygous A (risk) group showed decreased activation compared to G-allele carriers. Further, the functional connectivity analysis revealed a positive association of fronto-hippocampal connectivity with rs1006737 A alleles." [29]

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CACNA1C genotype explains interindividual differences in amygdala volume among patients with schizophrenia
http://www.ncbi.nlm.nih.gov/pubmed/23880959 [30]

"We were interested to investigate whether amygdala volumes differ between hemispheres, diagnostic or genotype groups, and whether any interactive effects exist. The CACNA1C genotype showed a significant effect on relative GM amygdala volume in patients with SZ. Our data suggest that the CACNA1C genotype may account for some heterogeneity in the effects of hemisphere and diagnosis on amygdala volume when comparing patients with SZ and controls and point to disturbed Ca^{2+}-signaling as a plausible mechanism contributing to the pathology in patients with SZ." [30]

L-type voltage-dependent Ca2+ channels mediate expression of presynaptic LTP in amygdala
http://www.ncbi.nlm.nih.gov/pubmed/19648911 [31]

"The molecular mechanisms underlying the expression of postsynaptic long-term potentiation (LTP) at glutamatergic synapses are well understood. However, little is known about those that mediate the expression of presynaptic LTP. We found that presynaptic LTP at cortical inputs to the lateral amygdala was blocked and reversed by L-type voltage-dependent Ca(2+) channel (L-VDCC) blockers. Thus, a persistent increase in L-VDCC-mediated glutamate release underlies the expression of presynaptic LTP in the amygdala." [31]

Effects of the CACNA1C risk allele on neurocognition in patients with schizophrenia and healthy individuals
http://www.ncbi.nlm.nih.gov/pubmed/22957138 [32]

"Recent genetic association studies have identified the A-allele of rs1006737 within CACNA1C as a risk factor for schizophrenia as well as mood disorders. In patients, A-allele carriers demonstrated significantly worse logical memory performance than the G-allele homozygotes." [32]

The CACNA1C risk allele selectively impacts on executive function in bipolar type I disorder
http://www.ncbi.nlm.nih.gov/pubmed/23406546 [33]

"A single nucleotide polymorphism (SNP) (rs1006737) in the CACNA1C gene has been strongly associated with increased risk for Bipolar disorder (BD) in genome-wide association studies. In patients with BD, the CACNA1C genotype Met/Met was associated with worse performance on all four executive function tests compared to Val/Val." [33]

Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression
http://www.ncbi.nlm.nih.gov/pubmed/21903025 [34]
Efficacy of omega-3 fatty acids in mood disorders - a systematic review and metaanalysis
http://www.ncbi.nlm.nih.gov/pubmed/19752840 [35]
A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression
http://www.ncbi.nlm.nih.gov/pubmed/20452573 [36]
Omega-3 polyunsaturated fatty acids for major depressive disorder
http://www.ncbi.nlm.nih.gov/pubmed/24083675 [37]

"The findings of 5 pooled datasets (n = 291) on the outcome of bipolar depression revealed a significant effect in favor of omega-3 (p = .029), with a moderate effect size of 0.34. The meta-analytic findings provide strong evidence that bipolar depressive symptoms may be improved by adjunctive use of omega-3. The evidence, however, does not support its adjunctive use in attenuating mania." [34-37]

1.3 Gene Tested: Sodium Channel Component, Ankyrin G (ANK3)

Molecular neurobiological clues to the pathogenesis of bipolar disorder
http://www.ncbi.nlm.nih.gov/pubmed/26210959 [14]

"Bipolar disorder is a serious psychiatric disorder, with a high heritability and unknown pathogenesis. Recent genome-wide association studies have identified the first loci, implicating genes such as CACNA1C and ANK3. The genes highlight several pathways, notably calcium signalling, as being of importance. Molecular studies suggest that the risk variants impact on gene regulation and expression." [14]

Ankyrin-G regulates inactivation gating of the neuronal sodium channel, Nav1.6
http://www.ncbi.nlm.nih.gov/pubmed/16775201 [38]

"Ankyrin-G, a modular protein, plays a critical role in clustering voltage-gated sodium channels (Nav channels) in nodes of Ranvier and initial segments of mammalian neurons…These results suggest that ankyrin-G regulates neuronal excitability not only through clustering Nav channels but also by directly modifying their channel gating." [38]

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Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder
http://www.ncbi.nlm.nih.gov/pubmed/18711365 [16]

Evidence for single nucleotide polymorphisms and their association with bipolar disorder
http://www.ncbi.nlm.nih.gov/pubmed/24143106 [18]

Two variants in Ankyrin 3 (ANK3) are independent genetic risk factors for bipolar disorder
http://www.ncbi.nlm.nih.gov/pubmed/19088739 [39]

ANK3 as a risk gene for schizophrenia: new data in Han Chinese and meta analysis
http://www.ncbi.nlm.nih.gov/pubmed/23109352 [40]

Ankyrin 3: genetic association with bipolar disorder and relevance to disease pathophysiology
http://www.ncbi.nlm.nih.gov/pubmed/23025490 [41]

Analogous to CACNA1C, a number of GWAS have implicated a polymorphism in the ANK3 gene as a risk factor for the development of bipolar disorder. A study of 4,387 cases and 6,209 controls linked the ANK3 SNP with bipolar risk ($p = 9.1 \times 10(-9)$[16]. [16,18,39-41]

Genetic analysis of SNPs in CACNA1C and ANK3 gene with schizophrenia: A comprehensive meta-analysis
http://www.ncbi.nlm.nih.gov/pubmed/26227746 [23]

"Recently, genome-wide association studies (GWAS), meta-analyses, and replication studies focusing on bipolar disorder (BD) have implicated the α-1C subunit of the L-type voltage-dependent calcium channel (CACNA1C) and ankyrin 3 (ANK3) genes in BD. Based on the hypothesis that both schizophrenia (SZ) and BD may share some common genetic risk factors, we investigated the association of CACNA1C and ANK3 with SZ using meta-analytic techniques, combining all published data up to April 2015…In summary, our study provides further evidence for the positive association of CACNA1C and ANK3 with SZ. These results support the hypothesis that both SZ and BD share common genetic risk factors. Further research is needed to examine the functions of CACNA1C and ANK3, and their interacting partners in the molecular, developmental, and pathophysiological processes in SZ." [23]

What is the impact of genome-wide supported risk variants for schizophrenia and bipolar disorder on brain structure and function? A systematic review.
http://www.ncbi.nlm.nih.gov/pubmed/25858580 [25]

"The powerful genome-wide association studies (GWAS) revealed common mutations that increase susceptibility for schizophrenia (SZ) and bipolar disorder (BD), but the vast majority were not known to be functional or associated with these illnesses. To help fill this gap, their impact on human brain structure and function has been examined. We systematically discuss this output to facilitate its timely integration in the psychosis research field; and encourage reflection for future research." [25]

Genome-wide supported risk variant for bipolar disorder alters anatomical connectivity in the human brain
http://www.ncbi.nlm.nih.gov/pubmed/22079454 [42]

"A meta-analysis of genome-wide association studies as well as independent replications showed ankyrin 3 (*ANK3)* to be one of the best-supported risk genes for bipolar disorder. Using an imaging genetics approach employing diffusion tensor imaging in 88 healthy volunteers, we show decreased white matter integrity, indicated by lower fractional anisotropy and longitudinal diffusivity, in healthy carriers of the *ANK3* rs10994336 risk genotype in the anterior limb of the internal capsule. We are also able to show that the resulting alterations of cortical–striatal–thalamic circuits are related to impaired set-shifting and increased risk-taking." [42].

The effect of ANK3 bipolar-risk polymorphisms on the working memory circuitry differs between loci and according to risk-status for bipolar disorder
http://www.ncbi.nlm.nih.gov/pubmed/25711502 [43]

"We examined the effect of BD-risk polymorphisms at rs10994336 and rs9804190 on the working memory (WM) circuit using functional magnetic resonance imaging (fMRI) data obtained from euthymic patients with BD (n = 41), their psychiatrically healthy first-degree relatives (n = 25) and unrelated individuals without personal or family history of psychiatric disorders (n = 46) while performing the N-back task… This study provides new insights on the neurogenetic correlates of allelic variation at different genome-wide supported BD-risk associated ANK3 loci that support their involvement in BD and highlight the modulatory influence of increased background genetic risk for BD." [43]

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Genetic modulation of working memory deficits by ankyrin 3 gene in schizophrenia
http://www.ncbi.nlm.nih.gov/pubmed/24361380 [44]

"Neuropsychological endophenotype approach is an emerging strategy in schizophrenia research to understand and identify the functional importance of genetically transmitted, brain-based deficits present in this disorder. Accumulating evidence indicated that working memory deficit is a core neuropsychological dysfunction in schizophrenia and a primary endophenotype indexing the liability to develop schizophrenia…Our results indicated that genetic variation within ANK3 may exert gene-specific modulating effects on working memory deficits in schizophrenia." [44]

The cognitive impact of the ANK3 risk variant for bipolar disorder: initial evidence of selectivity to signal detection during sustained attention
http://www.ncbi.nlm.nih.gov/pubmed/21304963 [45]

"Abnormalities in cognition have been reported in patients with Bipolar Disorder (BD) and their first degree relatives, suggesting that susceptibility genes for BD may impact on cognitive processes. The risk allele T was associated with reduced sensitivity in target detection ($p = 0.0004$) and increased errors of commission ($p = 0.0018$) during sustained attention regardless of diagnosis. Our results suggest that allelic variation in ANK3 impacts cognitive processes associated with signal detection and this mechanism may relate to risk for BD." [45]

The ANK3 bipolar disorder gene regulates psychiatric-related behaviors that are modulated by lithium and stress
http://www.ncbi.nlm.nih.gov/pubmed/23237312 [46]
"Ankyrin 3 (ANK3) has been strongly implicated as a risk gene for bipolar disorder (BD) by recent genome-wide association studies of patient populations. RNA interference of Ank3 in hippocampus dentate gyrus induced a highly specific and consistent phenotype marked by decreased anxiety-related behaviors and increased activity during the light phase, which were attenuated by chronic treatment with the mood stabilizer lithium." [46]

Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression
http://www.ncbi.nlm.nih.gov/pubmed/21903025 [34]
Efficacy of omega-3 fatty acids in mood disorders - a systematic review and metaanalysis
http://www.ncbi.nlm.nih.gov/pubmed/19752840 [35]
A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression
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Omega-3 polyunsaturated fatty acids for major depressive disorder
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The findings of 5 pooled datasets ($n = 291$) on the outcome of bipolar depression revealed a significant effect in favor of omega-3 ($p = .029$), with a moderate effect size of 0.34. The meta-analytic findings provide strong evidence that bipolar depressive symptoms may be improved by adjunctive use of omega-3. The evidence, however, does not support its adjunctive use in attenuating mania. [34-37]

1.4 Gene Tested: Serotonin Receptor 2C (5HT2C)

5-HT(2C) receptor agonists and the control of appetite
http://www.ncbi.nlm.nih.gov/pubmed/22249823 [47]

"The role of serotonin (5-HT) in appetite control is well recognised. 5-HT drugs reduce food intake in rodents in a manner consistent with an enhancement of satiety. In humans, they have been shown to reduce caloric intake, an effect associated with reduced hunger and increased satiety. These effects appear to be mediated, at least in part, by the 5-HT(2C) receptor subtype." [47]

Low gene expression conferred by association of an allele of the 5-HT2C receptor gene with antipsychotic-induced weight gain
http://www.ncbi.nlm.nih.gov/pubmed/15741483[48]

"Association has been reported between the C allele of a -759C/T polymorphism in the promoter of the 5-HT2C receptor gene (HTR2C) and antipsychotic-induced weight gain, suggesting that polymorphic HTR2C expression influences this phenotype…All haplotypes containing the -759C allele showed less transcriptional activity than haplotypes containing the -759T allele…These findings suggest that the -759C allele is functional and results in relative underexpression of HTR2C. Reduced expression of HTR2C mRNA may underlie vulnerability to weight gain following antipsychotic treatment." [48]

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Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy
http://www.ncbi.nlm.nih.gov/pubmed/24151799 [7]

Clozapine-induced weight gain associated with the 5HT2C receptor −759C/T polymorphism
http://www.ncbi.nlm.nih.gov/pubmed/15635667 [49]

Pharmacogenetic Aspects of Antipsychotic Drug-induced Weight Gain - A Critical Review
http://www.ncbi.nlm.nih.gov/pubmed/23431082 [50]

Polymorphisms of the HTR2C gene and antipsychotic-induced weight gain: an update and meta-analysis.
http://www.ncbi.nlm.nih.gov/pubmed/21121776 [51]
Numerous studies have confirmed that the 5HT2C polymorphism is associated with increased weight gain in response to atypical antipsychotic medication regimens. The data suggest that the polymorphism results in an under-expression of this receptor, which has been associated with satiety signaling in the hypothalamus. Therefore, reduction in neural satiety signaling is the putative mechanism behind the increased weight gain. [7,49-51]

Second-generation antipsychotic medications: Pharmacology, administration, and comparative side effects
http://www.uptodate.com/contents/second-generation-antipsychotic-medications-pharmacology-administration-and-comparative-side-effects [52]

Side effects associated with second-generation antipsychotics include weight gain, diabetes and hyperlipidemia. These side effects vary across the class in relation to binding affinity at receptor sites. Risk for weight gain is highest with the use of Clozapine and Olanzapine, moderately high with Iloperidone, Paliperidone, Quetiapine and Risperidone, lower with Asenapine, and relatively absent with Aripiprazole, Lurasidone and Ziprasidone. Risk for Hypercholesterolemia is highest with the use of Clozapine, Olanzapine and Quetiapine, moderately high with Iloperidone, lower with Paliperidone and Risperidone and relatively absent with Aripiprazole, Asenapine, Lurasidone and Ziprasidone. [52]

The 5-HT2C receptor and antipsychotic induced weight gain – mechanisms and genetics
http://www.ncbi.nlm.nih.gov/pubmed/16785265 [53]

"We have been studying pharmacogenetic correlates and find that common 5-HT_{2C} receptor promoter region polymorphisms demonstrate strong associations with weight gain in two first episode psychotic samples. In both series, we have found further association of antipsychotic drug-induced weight gain with a common and functional polymorphism of the gene for leptin. Along with initial BMI, these two pharmacogenetic factors account for almost 30% of the variance in drug-induced weight gain. Interestingly, the 5-HT_{2C} polymorphism appears to determine levels of circulating leptin, providing a potential mechanism underlying the genetic association of the 5-HT_{2C} receptor with weight gain. We have undertaken functional studies of haplotypes of the 5-HT_{2C} promoter region and find the allele associated with protection from weight gain results in reduced promoter activity." [53]

Pharmacogenetics of second-generation antipsychotics
http://www.ncbi.nlm.nih.gov/pubmed/24897292 [54]

"This review considers pharmacogenetics of the so called 'second-generation' antipsychotics. Findings for polymorphisms replicating in more than one study are emphasized and compared and contrasted with larger-scale candidate gene studies and genome-wide association study analyses… This review considers pharmacogenetics of the so called 'second-generation' antipsychotics. Findings for polymorphisms replicating in more than one study are emphasized and compared and contrasted with larger-scale candidate gene studies and genome-wide association study analyses." [54]

Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles
http://www.ncbi.nlm.nih.gov/pubmed/17848919 [55]

"Atypical antipsychotic drugs offer several notable benefits over typical antipsychotics, including greater improvement in negative symptoms, cognitive function, prevention of deterioration, and quality of life, and fewer extrapyramidal symptoms (EPS). However, concerns about EPS have been replaced by concerns about other side effects, such as weight gain, glucose dysregulation and dyslipidemia…This review examines the potential contribution of different receptors to metabolic side effects associated with atypical antipsychotic treatment for all seven agents currently marketed in the United States (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone and clozapine) and another agent (bifeprunox) in clinical development at the time of this publication." [55]

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Antipsychotic induced weight gain: genetics, epigenetics, and biomarkers reviewed
http://www.ncbi.nlm.nih.gov/pubmed/25138234 [56]

"Antipsychotic-induced weight gain (AIWG) is a prevalent side effect of antipsychotic treatment, particularly with second generation antipsychotics, such as clozapine and olanzapine. At this point, there is virtually nothing that can be done to predict who will be affected by AIWG. However, hope for the future of prediction lies with genetic risk factors…Although there are significant findings in many other genes, the most consistently replicated findings are in the melanocortin 4 receptor (MC4R), the serotonin 2C receptor (HTR2C), the leptin, the neuropeptide Y (NPY) and the cannabinoid receptor 1 (CNR1) genes." [56]

Effects of myo-inositol supplementation in postmenopausal women with metabolic syndrome: a perspective, randomized, placebo-controlled study
http://www.ncbi.nlm.nih.gov/pubmed/20811299 [57]

Randomized, double blind placebo-controlled trial: effects of myo-inositol on ovarian function and metabolic factors in women with PCOS
http://www.ncbi.nlm.nih.gov/pubmed/18074942 [58]

Combination of inositol and alpha lipoic acid in metabolic syndrome-affected women: a randomized placebo-controlled trial
http://www.ncbi.nlm.nih.gov/pubmed/23981814 [59]

Several studies have demonstrated that women with PCOS and insulin resistance may benefit from inositol supplementation. Supplementation has been shown to increase insulin sensitivity, improved metabolic side effects, and promote weight loss. [57-59]

1.5 Gene Tested: Melanocortin 4 Receptor (MC4R)

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An Obesity Risk SNP (rs17782313) near the MC4R Gene Is Associated with Cerebrocortical Insulin Resistance in Humans
http://www.ncbi.nlm.nih.gov/pubmed/21773004 [60]

"Activation of melanocortin-4 receptor (MC4R) by insulin sensitive neurons is a central mechanism in body weight regulation, and genetic variants in the MC4R gene (e.g., rs17782313) are associated with obesity… Cerebrocortical theta activity was impaired in carriers of the obesity risk allele. Therefore, cerebral insulin resistance may contribute to the obesity effect of rs17782313." [60]

Evidence that multiple genetic variants of MC4R play a functional role in the regulation of energy expenditure and appetite in Hispanic children
http://www.ncbi.nlm.nih.gov/pubmed/19889825 [61]

"Melanocortin-4-receptor (MC4R) haploinsufficiency is the most common form of monogenic obesity; however, the frequency of MC4R variants and their functional effects in general populations remain uncertain… Seven rare SNPs in coding and 18 SNPs in flanking regions of MC4R were identified. MGA showed suggestive associations between MC4R variants and body size, adiposity, glucose, insulin, leptin, ghrelin, energy expenditure, physical activity, and food intake… This comprehensive investigation provides strong evidence that MC4R genetic variants are likely to play a functional role in the regulation of weight, not only through energy intake but through energy expenditure." [61]

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MC4R rs489693: a clinical risk factor for second generation antipsychotic-related weight gain?
http://www.ncbi.nlm.nih.gov/pubmed/23920449 [62]

"The rs489693 polymorphism near the MC4R gene was associated with SGA-related weight gain in a genome-wide association study. We tried to replicate these results in our independent naturalistic study population. From 341 Caucasian inpatients receiving at least one SGA drug (olanzapine, clozapine, risperidone, paliperidone, quetiapine or amisulpride), carriers homozygous for the rs489693 A-allele (n = 35) showed a 2.2 times higher weight increase (+2.2 kg) than carriers of the CC-genotype (+1 kg) after 4 wk of treatment (analysis of covariance, p = 0.039). We revealed an even stronger effect in a subpopulation without weight gain inducing co-medication (factor 3.1, +2.8 kg, p = 0.044, (n = 16 of 169)) and in first episode patients (factor 2.7, +2.7 kg, p = 0.017, (n = 13 of 86)). Our results confirm the rs489693 A-allele as a possible risk factor for SGA-related weight gain." [62]

Association between common variants near the melanocortin 4 receptor gene and severe antipsychotic drug-induced weight gain.
http://www.ncbi.nlm.nih.gov/pubmed/22566560 [63]

"Our genome-wide association study yielded 20 single-nucleotide polymorphisms at a single locus exceeding a statistical threshold of P<10(-5). This locus, near the melanocortin 4 receptor (MC4R) gene, overlaps a region previously identified by large-scale genome-wide association studies of obesity in the general population. Effects were recessive, with minor allele homozygotes gaining extreme amounts of weight during the 12-week trial. These results were replicated in 3 additional cohorts, with rs489693 demonstrating consistent recessive effects; meta-analysis revealed a genome-wide significant effect (P=5.59 X 10 (-12). Moreover, we observed consistent effects on related metabolic indices, including triglyceride, leptin, and insulin levels…These data implicate MC4R in extreme SGA-induced weight gain and related metabolic disturbances. A priori identification of high-risk subjects could lead to alternative treatment strategies in this population." [63]

Antipsychotic drugs and obesity
http://www.ncbi.nlm.nih.gov/pubmed/21185230 [64]

"Mechanisms underlying antipsychotic cardiometabolic adverse effects are incompletely understood. This hampers the identification of high-risk patients, low-risk antipsychotics and preventive/ameliorative treatments. Recent clinical, molecular and genetic data suggest that: (i) antipsychotic-naïve samples provide the greatest power for mechanistic studies; (ii) weight and metabolic effects can be discordant, pointing to overlapping and distinct mechanisms; (iii) antipsychotics affect satiety and energy homeostasis signaling; (iv) the specific peptides mediating these effects are unknown but probably overlap with those involved in idiopathic obesity; and (v) single nucleotide polymorphisms in genes encoding known neurotransmitter receptors and metabolic proteins are promising pharmacogenomic targets for countering adverse affects. However, sophisticated molecular studies and genome-wide association studies, ideally in antipsychotic-naïve/first episode samples, are needed to further advance the field." [64]

Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review
http://www.ncbi.nlm.nih.gov/pubmed/15998156 [65]

"Increasing numbers of reports concerning diabetes, ketoacidosis, hyperglycaemia and lipid dysregulation in patients treated with second-generation (or atypical) antipsychotics have raised concerns about a possible association between these metabolic effects and treatment with these medications. This comprehensive literature review considers the evidence for and against an association between glucose or lipid dysregulation and eight separate second-generation antipsychotics currently available in the US and/or Europe, specifically clozapine, olanzapine, risperidone, quetiapine, zotepine, amisulpride, ziprasidone and aripiprazole." [65]

1.6 Gene Tested: Dopamine 2 Receptor (DRD2)

Pharmacogenetics and antipsychotic treatment response
http://www.ncbi.nlm.nih.gov/pubmed/26076775 [66]

" Antipsychotic drugs are widely used in the treatment of schizophrenia and psychotic disorder. The lack of antipsychotic response and treatment-induced side-effects, such as neuroleptic syndrome, polydipsia, metabolic syndrome, weight gain, extrapyramidal symptoms, tardive dyskinesia or prolactin increase, are the two main reasons for non-compliance and increased morbidity in schizophrenic patients. During the past decades intensive research has been done in order to determine the influence of genetic variations on antipsychotics dosage, treatment efficacy and safety. The present work reviews the molecular basis of treatment response of schizophrenia." [66]

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DRD2 promoter region variation predicts antipsychotic-induced weight gain in first episode schizophrenia
http://www.ncbi.nlm.nih.gov/pubmed/20664489 [67]

"We… examined the relationship between -141C Ins/Del (rs1799732), a functional promoter region polymorphism in DRD2, and antipsychotic-induced weight gain in 58 first episode schizophrenia patients enrolled in a randomized trial of risperidone versus olanzapine. Carriers of the deletion allele (n=29) were compared with Ins/Ins homozygotes (noncarriers, n=29) in a mixed model encompassing 10 weight measurements over 16 weeks. Deletion allele carriers showed significantly more weight gain after 6 weeks of treatment regardless of assigned medication." [67]

Dopamine D2 receptor genetic variation and clinical response to antipsychotic drug treatment: A meta-analysis
http://www.ncbi.nlm.nih.gov/pubmed/20194480 [68]

"There was a significant difference in response rate between the Del carrier vs. Ins/Ins genotypes (pooled OR = 0.65, 95% CI = 0.43 ~ 0.97, p = 0.03), indicating that Del carriers tend to have less favorable antipsychotic drug responses than patients with the Ins/Ins genotype." [68]

Association of variants in DRD2 and GRM3 with motor and cognitive function in first-episode psychosis
http://www.ncbi.nlm.nih.gov/pubmed/24682224 [69]

"Eighty three patients were followed after 6 weeks of antipsychotic treatment. At baseline, patients with a -141C deletion in DRD2 rs1799732 had slower initiation eye velocity and longer pursuit latency than CC insertion carriers… Antipsychotic treatment resulted in prolonged pursuit latency in DRD2 rs1799732_CC insertion carriers and a decline in pursuit maintenance in GRM3 rs6465084_GG carriers. The present study demonstrates for the first time that neurophysiological measures of motor and neurocognitive deficits in patients with psychotic disorders have different associations with genes regulating dopamine and glutamate systems, respectively. Alterations in striatal D2 receptor activity through the -141C Ins/Del polymorphism could contribute to pursuit initiation deficits in psychotic disorders." [69]

1.7 Gene Tested: Catechol-O-Methyltransferase (COMT; Val/Val genotype)

Effect of COMT val158met genotype on cognition and personality
http://www.ncbi.nlm.nih.gov/pubmed/18755576 [70]

"The gene encoding catechol-O-methyltransferase (COMT), an enzyme which regulates prefrontal cortex dopamine, contains a common functional single nucleotide polymorphism (val158met, rs4680G/A), which accounts for part of the interindividual variance in performance during working memory tasks and also predicts personality traits. We examined the relationship between the val158met polymorphism and cognitive function as well as personality traits in 522 healthy individuals (mean age: 24.75 years, SD=5.84, mean years of education: 15.59, SD=2.65). COMT val158met genotype was related in allele dosage fashion to performance in an executive function test, with the met/met carriers scoring highest." [70]

Neurogenetics and pharmacology of learning, motivation, and cognition
http://www.ncbi.nlm.nih.gov/pubmed/20631684 [71]

"Many of the individual differences in cognition, motivation, and learning-and the disruption of these processes in neurological conditions-are influenced by genetic factors. We provide an integrative synthesis across human and animal studies, focusing on a recent spate of evidence implicating a role for genes controlling dopaminergic function in fronto-striatal circuitry, including COMT, DARPP-32, DAT1, DRD2, and DRD4." [71]

Effects of the catechol-O-methyltransferase Val158Met polymorphism on executive function: a meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls
http://www.ncbi.nlm.nih.gov/pubmed/17325717 [72]

"The catechol-O-methyltransferase (COMT) Val(158)Met polymorphism is hypothesized to affect executive function in patient and control populations. Twelve studies met inclusion criteria (total n=1910) providing 10 samples each of patients and controls. In healthy controls, individuals with the Met/Met genotype performed better than those with the Val/Val genotype (d=0.29; 95% confidence interval (CI) 0.02-0.55; P=0.03)." [72]

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Inverted-U-shaped dopamine actions on human working memory and cognitive control
http://www.ncbi.nlm.nih.gov/pubmed/21531388 [73]

"First, the existence of an optimum DA level for cognitive function implicates the need to take into account baseline levels of DA when isolating the effects of DA. Second, cognitive control is a multifactorial phenomenon, requiring a dynamic balance between cognitive stability and cognitive flexibility." [73]

Role of dopamine in the motivational and cognitive control of behavior
http://www.ncbi.nlm.nih.gov/pubmed/18660464 [74]

"Brain dopamine has often been implicated in impulsive and/or inflexible behaviors, which may reflect failures of motivational and/or cognitive control. However, the precise role of dopamine in such failures of behavioral control is not well understood...In addition, there are large individual differences in the response to dopaminergic drugs with some individuals benefiting from and others being impaired by the same drug. This complicates progress in the understanding of dopamine's role in behavioral control processes, but also provides a major problem for neuropsychiatry, where some individuals are disproportionately vulnerable to the adverse effects of dopamine-enhancing drugs on motivation and cognition." [74]

Treatment of cognitive deficits associated with schizophrenia: potential role of catechol-O-methyltransferase inhibitors
http://www.ncbi.nlm.nih.gov/pubmed/17579498 [75]

"… individuals with the Val/Val genotype, which encodes for the high-activity enzyme resulting in lower dopamine concentrations in the prefrontal cortex, perform less well and are less efficient physiologically than Met/Met individuals. These findings raise the possibility of new pharmacological interventions for the treatment of prefrontal cortex dysfunction and of predicting outcome based on COMT genotype. One strategy consists of the use of CNS-penetrant COMT inhibitors such as tolcapone. A second strategy is to increase extracellular dopamine concentrations in the frontal cortex by blocking the noradrenaline (norepinephrine) reuptake system… A third possibility involves the use of modafinil, a drug with an unclear mechanism of action but with positive effects on working memory in rodents. The potential of these drugs to improve executive cognitive function by selectively increasing dopamine load in the frontal cortex but not in subcortical territories, and the possibility that response to them may be modified by a COMT polymorphism, provides a novel genotype-based targeted pharmacological approach without abuse potential for the treatment of cognitive disorder in schizophrenia and in other conditions involving prefrontal cortex dysfunction." [75]

COMT genotype and response to cognitive remediation in schizophrenia
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"This study evaluated the association of the COMT Val108/158 Met genotype with response to computerized neurocognitive remediation (CRT)… The low activity Met allele (Met/Met; Val/Met) was associated with significantly greater improvements in the MATRICS domains of Verbal Learning, Visual Learning and Attention/Vigilance after CRT." [76]

Catechol-O-methyltransferase val158met genotype modulates sustained attention in both the drug-free state and in response to amphetamine
http://www.ncbi.nlm.nih.gov/pubmed/20414144 [77]

"The results of this study extend earlier findings with the COMT genotypes to additional measures of cognition, and suggest that the presence of the val allele is associated with poorer performance and greater improvement with a stimulant drug." [77]

Tolcapone improves cognition and cortical information processing in normal human subjects
http://www.ncbi.nlm.nih.gov/pubmed/17063156 [78]

"We found significant drug effects on measures of executive function and verbal episodic memory, individuals with val/val genotypes improved, whereas individuals with met/met genotypes worsened on tolcapone." [78]

The effect of repetitive transcranial magnetic stimulation on monoamine outflow in the nucleus accumbens shell in freely moving rats
http://www.ncbi.nlm.nih.gov/pubmed/22771976 [79]

"Here, we study the effects of acute repetitive transcranial magnetic stimulation on monoamine outflow in the nucleus accumbens shell in awake and freely moving rats using in vivo microdialysis. To scale the biochemical results to the induced electric field in the rat brain, we obtained a realistic simulation of the stimulation scenario using a finite element model. Applying 20 Hz repetitive transcranial magnetic stimulation in 6 trains of 50 stimuli with 280 µs pulse width at a magnetic field strength of 130% of the individual motor threshold, dopamine as well as serotonin outflow in the nucleus accumbens shell significantly increased compared to sham stimulation." 79

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rTMS of the left dorsolateral prefrontal cortex modulates dopamine release in the ipsilateral anterior cingulate cortex and orbitofrontal cortex.

http://www.ncbi.nlm.nih.gov/pubmed/19696930 [80]

"Brain dopamine is implicated in the regulation of movement, attention, reward and learning and plays an important role in Parkinson's disease, schizophrenia and drug addiction. Animal experiments have demonstrated that brain stimulation is able to induce significant dopaminergic changes in extrastriatal areas. Given the up-growing interest of non-invasive brain stimulation as potential tool for treatment of neurological and psychiatric disorders, it would be critical to investigate dopaminergic functional interactions in the prefrontal cortex and more in particular the effect of dorsolateral prefrontal cortex (DLPFC) (areas 9/46) stimulation on prefrontal dopamine (DA). To our knowledge, this is the first study to provide evidence of extrastriatal DA modulation following acute rTMS of DLPFC with its effect limited to the specific areas of medial prefrontal cortex. [(11)C]FLB 457-PET combined with rTMS may allow to explore the neurochemical functions of specific cortical neural networks and help to identify the neurobiological effects of TMS for the treatment of different neurological and psychiatric diseases." [80]

Should We Expand the Toolbox of Psychiatric Treatment Methods to Include Repetitive Transcranial Magnetic Stimulation (rTMS)? A Meta-Analysis of the Efficacy of rTMS in Psychiatric Disorders

http://www.ncbi.nlm.nih.gov/pubmed/20361902 [81]

Baseline Brain Metabolism in Resistant Depression and Response to Transcranial Magnetic Stimulation

http://www.ncbi.nlm.nih.gov/pubmed/21849980 [82]

Safety, Tolerability, and Effectiveness of High Doses of Adjunctive Daily Left Prefrontal Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression in a Clinical Setting

http://www.ncbi.nlm.nih.gov/pubmed/21343710 [83]

HF-rTMS Treatment in Medication-Resistant Melancholic Depression: Results from 18FDG-PET Brain Imaging

http://www.ncbi.nlm.nih.gov/pubmed/19890238 [84]

The expanding evidence base for rTMS treatment of depression

http://www.ncbi.nlm.nih.gov/pubmed/23154644 [85]

There have been a number of studies which indicate that Repetitive Transcranial Magnetic Stimulation (rTMS) is effective in reducing symptoms in treatment-resistant depression (TRD). A meta-analysis for rTMS concluded it may be time to utilize rTMS as a clinical treatment method for depression, for auditory verbal hallucinations, and possibly for negative symptoms [81]. Another review of several studies found, "recent studies suggest that daily left prefrontal TMS over several weeks as a treatment for depression not only appears to have efficacy in rigorous randomized controlled trials, but is effective in real-world settings, with remission in 30-40% of patients [85]." [81-85]

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1.9 Gene Test: Alpha-2A Adrenergic Receptor (ADRA2A)

Alpha-2 adrenergic receptors and attention-deficit/hyperactivity disorder
http://www.ncbi.nlm.nih.gov/pubmed/20652773 [86]

"In the following review, we consider relevant neurobiological underpinnings of ADHD with respect to why alpha-2 agents may be effective in treating this condition. We also review new formulations of alpha-2 agonists, emerging data on their use in ADHD, and implications for clinical practice. Integrating knowledge of pathophysiologic mechanisms and mechanisms of drug action may inform our medication choices and facilitate treatment of ADHD and related disorders." [86]

Regional differences in cerebral perfusion associated with the alpha-2A-adrenergic receptor genotypes in attention deficit hyperactivity disorder
http://www.ncbi.nlm.nih.gov/pubmed/20731965 [87]

"Our findings suggest that regional differences in cerebral perfusion in the orbitofrontal cortex represent an intermediate neuroimaging phenotype associated with the ADRA2A MspI polymorphism; these data support the validity of the noradrenergic hypothesis regarding the pathophysiology of ADHD." [87]

The use of α-2A adrenergic agonists for the treatment of attention-deficit/hyperactivity disorder
http://www.ncbi.nlm.nih.gov/pubmed/20925474 [88]

"Neuropsychiatric disorders involve dysfunction of the prefrontal cortex (PFC), a highly evolved brain region that mediates executive functioning…Imaging studies have shown reduced PFC gray matter, weaker PFC connections and altered PFC function in patients with attention-deficit/hyperactivity disorder. Thus, medications that strengthen PFC network connections may be particularly useful for the treatment of attention-deficit/hyperactivity disorder and related disorders. Recent data show that compounds such as guanfacine can enhance PFC function by stimulating postsynaptic α-2A receptors on the dendritic spines of PFC pyramidal cells where networks interconnect." [88]

Clinical utility of guanfacine extended release in the treatment of ADHD in children and adolescents
http://www.ncbi.nlm.nih.gov/pubmed/26170637 [89]

"In the US, one available nonstimulant option is guanfacine extended release (XR). As a selective α2A adrenergic receptor, guanfacine acts on the central noradrenergic pathways and cortical noradrenergic targets to improve working memory and attention… Available data also indicate that guanfacine XR is superior to atomoxetine and is as effective as the nonselective α2 adrenergic receptor agonist, clonidine XR… This review discusses the clinical efficacy and patient preference of guanfacine XR based on available published data on the safety, relative effectiveness, and tolerance of this medication to treat ADHD." [89]

Methylphenidate improves prefrontal cortical cognitive function through alpha2 adrenoceptor and dopamine D1 receptor actions: Relevance to therapeutic effects in Attention Deficit Hyperactivity Disorder
http://www.ncbi.nlm.nih.gov/pubmed/15916700 [90]

"Methylphenidate (MPH) produced an inverted U dose response whereby moderate doses (1.0-2.0 mg/kg, p.o.) significantly improved delayed alternation performance, while higher doses (2.0-3.0 mg/kg, p.o.) produced perseverative errors in many animals. The enhancing effects of MPH were blocked by co-administration of either the alpha2 adrenoceptor antagonist, idazoxan, or the dopamine D1 antagonist, SCH23390, in doses that had no effect on their own." [90]

Norepinephrine genes predict response time variability and methylphenidate-induced changes in neuropsychological function in attention deficit hyperactivity disorder.
http://www.ncbi.nlm.nih.gov/pubmed/23609393 [91]

"The aim of this study was to examine the relationship between polymorphisms in the α-2A-adrenergic receptor (ADRA2A) and norepinephrine transporter (SLC6A2) genes and attentional performance in ADHD children before and after pharmacological treatment…After medication, increasing possession of a G allele at the MspI polymorphism of the ADRA2A gene was associated with increased MPH-related change in response time variability in the flanker task (P = 1.0 × 10). Our study suggested an association between norepinephrine gene variants and response time variability measured at baseline and after MPH treatment in children with ADHD." [91]

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Adrenergic alpha2A receptor gene and response to methylphenidate in attention-deficit/hyperactivity disorder-predominantly inattentive type.

http://www.ncbi.nlm.nih.gov/pubmed/18200436 [92]

"In this naturalistic pharmacogenetic study, 59 subjects with ADHD-I from a non-referred sample were treated with short-acting methylphenidate and genotyped for ADRA2A -1291 C > G polymorphism. The primary outcome measure was the inattentive subscale of the SNAP-IV applied by a child psychiatrist blinded to genotype at baseline and first month of treatment. Children and adolescents with the G allele showed significantly lower inattentive scores with MPH treatment at the first month of treatment than subjects without the G allele (n = 59; F = 6.14; p = 0.016). We extended to ADHD-I previous findings suggesting the influence of the G allele at the ADRA2A -1291 C > G polymorphism on the improvement of inattentive symptoms with methylphenidate in children with all ADHD subtypes." [92]

Association of the adrenergic alpha2A receptor gene with methylphenidate improvement of inattentive symptoms in children and adolescents with attention-deficit/hyperactivity disorder.

http://www.ncbi.nlm.nih.gov/pubmed/17283289 [93]

"To evaluate the association between the ADRA2A -1291 C>G polymorphism and the clinical response to methylphenidate treatment in children and adolescents with ADHD. A significant interaction effect between the presence of the G allele and treatment with methylphenidate over time on inattentive scores was detected during the 3 months of treatment (n = 106; F(2,198) = 4.30; P = .02). We documented the effect of the G allele at the ADRA2A -1291 C>G polymorphism on the improvement of inattentive symptoms with methylphenidate treatment in children and adolescents with ADHD. Our findings provide clinical evidence for the involvement of the noradrenergic system in the modulation of methylphenidate action." [93]

1.10 Gene Tested: Methylenetetrahydrofolate Reductase (MTHFR)

L-Methylfolate: A Vitamin for Your Monoamines

http://www.ncbi.nlm.nih.gov/pubmed/19193337 [94]

Vitamins, Monoamines, and Depression

http://primarypsychiatry.com/vitamins-monoamines-and-depression/ [95]

"Synthesis of the three monoamine neurotransmitters, serotonin, dopamine, and norpepinephrine, is regulated by L-methylfolate [94]." "There are several mechanisms by which folate may affect central nervous system (CNS) pathways implicated in the depressive disorders. Biopterin, which is dependent on L-methylfolate for synthesis, serves as an essential co-factor for converting phenylalanine to tyrosine, and for hydroxylation of tyrosine and tryptophan to yield dopamine, norepinephrine, and serotonin." [95]

Association between MTHFR C677T polymorphism and depression: An updated meta-analysis of 26 studies

http://www.ncbi.nlm.nih.gov/pubmed/23831680 [96]

"Previous studies concerning the association between the 5,10-methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphism and depression have provided inconclusive findings. This meta-analysis recruited 26 published studies which were selected by a search of electronic databases up to January 2013, including 4992 depression cases and 17,082 controls. Meta-analyses results suggested that MTHFR C677T polymorphism contributed to the increased depression risk in overall populations (for T vs. C: OR=1.19, 95%CI=1.07-1.32; for TT+CT vs. CC: OR=1.15, 95%CI=1.01-1.31; for TT vs. CC: OR=1.42, 95%CI=1.16-1.75; for TT vs. CT+CC: OR=1.38, 95%CI=1.16-1.63)." [96]

Methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms and psychiatric disorders: a HuGE review

http://www.ncbi.nlm.nih.gov/pubmed/17074966 [97]

"The authors performed a meta-analysis of studies examining the association between polymorphisms in the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene, including MTHFR C677T and A1298C, and common psychiatric disorders, including unipolar depression, anxiety disorders, bipolar disorder, and schizophrenia. The primary comparison was between homozygote variants and the wild type for MTHFR C677T and A1298C... This meta-analysis demonstrates an association between the MTHFR C677T variant and depression, schizophrenia, and bipolar disorder, raising the possibility of the use of folate in treatment and prevention." [97]

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Meta-analysis of MTHFR gene variants in schizophrenia, bipolar disorder and unipolar depressive disorder: evidence for a common genetic vulnerability?

http://www.ncbi.nlm.nih.gov/pubmed/21185933 [98]

> "We conducted a meta-analysis of all published case-control studies investigating associations between two common MTHFR single nucleotide polymorphisms (SNPs), MTHFR C677T (sample size 29,502) and A1298C (sample size 7934), and the major psychiatric disorders (i) schizophrenia (SZ), (ii) bipolar disorder (BPD), and (iii) unipolar depressive disorder (UDD)…MTHFR C677T was significantly associated with all of the combined psychiatric disorders (SZ, BPD and UDD); random effects odds ratio (OR)=1.26 for TT versus CC genotype carriers; confidence interval (CI) 1.09-1.46); meta-regression did not suggest moderating effects of psychiatric diagnosis, sex, ethnic group or year of publication. Although MTHFR A1298C was not significantly associated with the combination of major psychiatric disorders, nor with SZ, there was evidence for diagnostic moderation indicating a significant association with BPD (random effects OR=2.03 for AA versus CC genotype carriers, CI: 1.07-3.86). Meta-analysis on UDD was not possible due to the small number of studies available. This study provides evidence for shared genetic vulnerability for SZ, BPD and UDD mediated by MTHFR 677TT genotype, which is in line with epigenetic involvement in the pathophysiology of these psychiatric disorders." [98]

L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials

http://www.ncbi.nlm.nih.gov/pubmed/23212058 [99]

L-methylfolate Plus SSRI or SNRI from Treatment Initiation Compared to SSRI or SNRI Monotherapy in a Major Depressive Episode

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3036555/ [100]

> Several studies have demonstrated l-methylfolate as an effective augmentation strategy with SSRI/SNRIs. [99,100]

Comparative assessment of adherence measures and resource use in SSRI/SNRI-treated patients with depression using second-generation antipsychotics or L-methylfolate as adjunctive therapy

http://www.ncbi.nlm.nih.gov/pubmed/24372461 [101]

> "Patients who augmented SSRI/SNRI therapy with second-generation atypical antipsychotics (SGA) or L-methylfolate achieved modified application of the HEDIS (mHEDIS) acute medication management (AMM) acute phase and continuation phase adherence scores of 69%-79% and 50%-62%, respectively. These modified scores exceeded the 2012 national median benchmarks for unmodified HEDIS AMM measures for commercial health plans. In this study, augmentation with L-methylfolate was associated with significantly higher adherence measures compared with augmentation with SGA. In addition, health care utilization and total health care costs, as well as depression-related costs, were significantly lower in the L-methylfolate augmentation group compared with augmentation with SGA." [101]

Effect of adjunctive L-methylfolate 15 mg among inadequate responders to SSRIs in depressed patients who were stratified by biomarker levels and genotype: results from a randomized clinical trial.

http://www.ncbi.nlm.nih.gov/pubmed/24813065 [102]

> "The objective of the current post hoc analysis was to evaluate the effect of specific biological and genetic markers on the antidepressant efficacy of adjunctive L-methylfolate 15 mg versus placebo from a trial of inadequate responders to selective serotonin reuptake inhibitors (SSRIs)… Biomarkers associated with inflammation or metabolism and genomic markers associated with L-methylfolate synthesis and metabolism may identify patients with SSRI-resistant depression who are responsive to adjunctive therapy with L-methylfolate 15 mg. Confirmatory studies are needed." [102]

1.11 Gene Tested: Brain-derived Neurotrophic Factor (BDNF)

The BDNF gene Val66Met polymorphism as a modifier of psychiatric disorder susceptibility: progress and controversy

http://www.ncbi.nlm.nih.gov/pubmed/25824305 [103]

> "A single-nucleotide polymorphism in the proregion of BDNF, termed the Val66Met polymorphism, results in deficient subcellular translocation and activity-dependent secretion of BDNF, and has been associated with impaired neurocognitive function in healthy adults and in the incidence and clinical features of several psychiatric disorders…Here we comprehensively review the role and relevance of the Val66Met polymorphism in psychiatric disorders, with emphasis on suicidal behavior and anxiety, eating, mood and psychotic disorders." [103]

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Genetic and epigenetic regulation of the brain-derived neurotrophic factor in the central nervous system

http://www.ncbi.nlm.nih.gov/pubmed/24910563 [104]

> "BDNF is required for the development and proper function of the central nervous system, where it is involved in a variety of neural and molecular events relevant to cognition, learning, and memory processes… The present essay aims to summarize the published information on the matter, emphasizing their possible implications in health and disease or in the treatment of different neurologic and psychiatric disorders." [104]

Meta-analysis of the BDNF Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity

http://www.ncbi.nlm.nih.gov/pubmed/18852698 [105]

Interaction between stress and the BDNF Val66Met polymorphism in depression: a systematic review and meta-analysis

http://www.ncbi.nlm.nih.gov/pubmed/24433458 [106]

> Several meta-analyses have demonstrated the BDNF polymorphism Val66Met (rs6265) is associated with major depression and mood-related phenotypes. Results have demonstrated that there may be differential impact of the polymorphism between the sexes and across ethnicities; however these associations need to be confirmed in future studies. BDNF has been shown to moderate the relationship between life stress and depression. Results have also shown that Met carriers have an increased risk for geriatric depression compared to Val/Val homozygotes. These meta-analyses demonstrate the importance of BDNF polymorphisms in depression and treatment response. [105,106]

The brain-derived neurotrophic-factor (BDNF) val66met polymorphism is associated with geriatric depression: a meta-analysis

http://www.ncbi.nlm.nih.gov/pubmed/22610920 [107]

> "Genetic association studies of the BDNF Val66Met polymorphism (rs6265) in geriatric depression have produced inconsistent results. A meta-analysis of studies was conducted to compare the frequency of the BDNF Val66Met variant between cases with geriatric depression and age-matched controls. A total of five studies involving 523 cases with geriatric depression and 1,220 psychiatrically healthy controls was included. Met allele carriers had an increased risk for geriatric depression when compared to Val/Val homozygotes (P = 0.004, OR = 1.48, 95% CI = 1.13-1.93). Our findings suggest the BDNF Met allele may confer increased risk for depression as individual age." [107]

BDNF gene polymorphism (Val66Met) predicts amygdala and anterior hippocampus responses to emotional faces in anxious and depressed adolescents

http://www.ncbi.nlm.nih.gov/pubmed/19931400 [108]

> "The current study investigated the association between BDNF genotype and amygdala-hippocampal responses to emotional stimuli in adolescents with anxiety disorders and/or major depressive disorder (MDD) and in healthy adolescents…Greater activations in patients than healthy adolescents were found. Critically, these hyperactivations were modulated by BDNF genotype: Met-carriers showed greater neural responses of emotional faces than Val/Val homozygotes in patients only. These data are first to demonstrate the contribution of BDNF gene variants to the neural correlates of adolescent anxiety and depression. Early "gene-brain" linkages may lay the foundation for longer-term patterns of neural dysfunction in affective disorders." [108]

Impact of genetic variant BDNF (Val66Met) on brain structure and function

http://www.ncbi.nlm.nih.gov/pubmed/18497103 [109]

> "…We generated a variant BDNF mouse (BDNF(MET/Met)) that reproduces the phenotypic hallmarks in humans with the variant allele. Variant BDNF(Met) was expressed in brain at normal levels, but its secretion from neurons was defective… When placed in conflict settings, BDNF(Met/Met) mice display increased anxiety-related behaviours that were not normalized by the antidepressant, fluoxetine. A genetic variant BDNF may thus play a key role in genetic predispositions to anxiety and depressive disorders." [109]

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Predicting change in symptoms of depression during the transition to university: the roles of BDNF and working memory capacity

http://www.ncbi.nlm.nih.gov/pubmed/24920443 [110]

"The present study has provided the first examination of whether working memory capacity, the BDNF Val66Met polymorphism, and their interaction predict changes in symptoms of depression during the transition to university… The BDNF Val66Met polymorphism, however, moderated the association between working memory capacity and symptom change. Among met carriers, lower working memory capacity in the presence of negative-but not neutral-distractors was associated with increased symptoms of depression over the semester. For the val/val group, working memory capacity did not predict symptom change. These findings contribute directly to biological and cognitive models of depression and highlight the importance of examining Gene × Cognition interactions when investigating risk for depression." [110]

Functional and structural specific roles of activity-driven BDNF within circuits formed by single spiny stellate neurons of the barrel cortex

http://www.ncbi.nlm.nih.gov/pubmed/25414642 [111]

"Val66Met polymorphism of BDNF may be associated with increased risk for cognitive impairments and is mediated at least in part by activity-dependent trafficking and/or secretion of BDNF. Using mutant mice that lacked activity-driven BDNF expression (bdnf-KIV), we previously reported that experience regulation of the cortical GABAergic network is mediated by activity-driven BDNF expression. Here, we demonstrate that activity-driven BDNF's effects on circuits formed by the layer IV spiny stellate cells are highly specific." [111]

Valence-specific effects of BDNF Val66Met polymorphism on dopaminergic stress and reward processing in humans

http://www.ncbi.nlm.nih.gov/pubmed/24760847 [112]

"Neuroimaging results revealed a significant effect of BDNF (Met(66) carriers > Val/Val) on brain responses during the anticipation of monetary losses, baseline D2/3 receptor availability, and pain-stress-induced DA release in the NAc. Conversely, BDNF Met(66) carriers showed no activation in response to monetary gains and a blunted DA response to the analgesic placebo in the NAc. These results provide initial human evidence regarding the effect of the BDNF Val(66)Met polymorphism on DA-mediated responses to stress, its cognitive regulation by positive expectations, and the anticipatory responses to monetary gains and losses in the VTA-NAc pathway. Our results are of relevance to the neurobiology of stress and reward interactions and the pathophysiology of stress-related disorders." [112]

Variant brain-derived neurotrophic factor Val66Met polymorphism alters vulnerability to stress and response to antidepressants

http://www.ncbi.nlm.nih.gov/pubmed/22442074 [113]

"Brain-derived neurotrophic factor (BDNF) plays important roles in cell survival, neural plasticity, learning, and stress regulation…We found that heterozygous BDNF(+/Met) mice displayed hypothalamic-pituitary-adrenal axis hyperreactivity, increased depressive-like and anxiety-like behaviors, and impaired working memory compared with WT mice after 7 d restraint stress. Moreover, BDNF(+/Met) mice exhibited more prominent changes in BDNF levels and apical dendritic spine density in the prefrontal cortex and amygdala after stress, which correlated with the impaired working memory and elevated anxiety-like behaviors. Finally, the depressive-like behaviors in BDNF(+/Met) mice could be selectively rescued by acute administration of desipramine but not fluoxetine. These data indicate selective behavioral, molecular, and structural deficits resulting from the interaction between stress and the human genetic BDNF(Met) polymorphism. Importantly, desipramine but not fluoxetine has antidepressant effects on BDNF(+/Met) mice, suggesting that specific classes of antidepressant may be a more effective treatment option for depressive symptoms in humans with this genetic variant BDNF." [113]

Effects of BDNF polymorphisms on antidepressant action

http://www.ncbi.nlm.nih.gov/pubmed/21253406 [114]

"In human BDNF gene, there is a common functional polymorphism (Val66Met) in the pro-region of BDNF, which affects the intracellular trafficking of proBDNF. A recent meta-analysis of eight studies, which included data from 1,115 subjects, suggested that the Val/Met carriers have increased antidepressant response in comparison to Val/Val homozygotes, particularly in the Asian population. The positive molecular heterosis effect (subjects heterozygous for a specific genetic polymorphism show a significantly greater effect) is compatible with animal studies showing that, although BDNF exerts an antidepressant effect, too much BDNF may have a detrimental effect on mood. Several recommendations are proposed for future antidepressant pharmacogenetic studies of BDNF, including the consideration of multiple polymorphisms and a haplotype approach, gene-gene interaction, a single antidepressant regimen, controlling for age and gender interactions, and pharmacogenetic effects on specific depressive symptom-clusters." [114]

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Meta-analysis of BDNF Val66Met polymorphism association with treatment response in patients with major depressive disorder

http://www.ncbi.nlm.nih.gov/pubmed/20167454 [115]

"The aim of our meta-analysis was to assess the association between BDNF Val66Met polymorphism and treatment response in patients with MDD…a significant association of Val/Met genotype and increased response rate was found in comparison to Val/Val in overall population (OR=1.66, 95%CI=1.07-2.57, P=0.02). In the subgroup analysis, similar result was shown in Asian population (OR=1.83, 95%CI=1.03-3.26, P=0.04), but not in Caucasian population. We didn't observe a significant association of BDNF Val66Met polymorphism with remission rate. This meta-analysis demonstrates the association between BDNF Val66Met polymorphism and treatment response in patients with MDD, and Val66Met heterozygous patients have a better response rate in comparison to Val/Val homozygote patients, especially in Asian population." [115]

Brain-derived neurotrophic factor Val66Met polymorphism and 6-month antidepressant remission in depressed Caucasian patients

http://www.ncbi.nlm.nih.gov/pubmed/25658497 [116]

"We assessed the impact of Val66Met polymorphism on antidepressant response and remission depending on antidepressant classes…With SSRI, Val/Val patients had a higher response rate 3 months post-treatment than Met patients (68.1% versus 44%; adjusted-OR: 3.04, IC95% [1.05; 9.37], p=0.04). With SNRI/TCA, Val/Val patients had a lower remission rate 6 months post-treatment than Met patients (33.3% versus 60.9%, adjusted-OR: 0.27, IC95% [0.09; 0.76], p=0.02). This study argues for a personalized prescription of antidepressants in Caucasian patients with major depressive disorder, based on the BDNF Val66Met polymorphism: SSRI should be preferred for Val/Val patients and SNRI/TCA for Met patients. Further studies are required to confirm these data." [116]

BDNF and CREB1 genetic variants interact to affect antidepressant treatment outcomes in geriatric depression

http://www.ncbi.nlm.nih.gov/pubmed/23619509 [117]

"These results provide new evidence for the importance of the BDNF pathway in antidepressant response in geriatric patients. The negative effect of the Met66 allele on antidepressant outcomes is consistent with basic science findings indicating a negative effect of this variant on BDNF activity in the brain. Further, the effect of BDNF genetic variation on antidepressant treatment is modified by variation in the gene encoding the downstream effector CREB1." [117]

BDNF Val66Met impairs fluoxetine-induced enhancement of adult hippocampus plasticity

http://www.ncbi.nlm.nih.gov/pubmed/22218094 [118]

"BDNF(Met/Met) mice had decreased basal BDNF protein levels in the hippocampus that did not significantly increase following fluoxetine treatment. BDNF(Met/Met) mice had impaired survival of newly born cells and LTP in the dentate gyrus; the LTP effects remained blunted following fluoxetine treatment. The observed effects of the BDNF Val66Met SNP on hippocampal BDNF expression and synaptic plasticity provide a possible mechanistic basis by which this common BDNF SNP may impair efficacy of SSRI drug treatment." [118]

A behavioral analysis of the impact of voluntary physical activity on hippocampus-dependent contextual conditioning

http://www.ncbi.nlm.nih.gov/pubmed/19115374 [119]

"The current studies investigated the impact of voluntary wheel running on learning and memory for context and extinction using contextual fear conditioning which is known to be dependent on the hippocampus… The effect of wheel running on brain-derived neurotrophic factor (BDNF) messenger ribonucleic acid (mRNA) in hippocampal and amygdala subregions was also investigated. Wheel running increased BDNF mRNA in the dentate gyrus, CA1, and the basolateral amygdala. Results are consistent with improved hippocampal function following physical activity." [119]

The brain-derived neurotrophic factor Val66Met polymorphism moderates an effect of physical activity on working memory performance

http://www.ncbi.nlm.nih.gov/pubmed/23907543 [120]

"…carriers of the methionine-specifying (Met) allele of the brain-derived neurotrophic factor (BDNF) Val66Met polymorphism have reduced secretion of BDNF and poorer memory, yet physical activity increases BDNF levels…we evaluated participants' performance on a battery of tests assessing memory, learning, and executive processes, and evaluated their physical activity with the Paffenbarger Physical Activity Questionnaire. BDNF genotype interacted robustly with physical activity to affect working memory, but not other areas of cognitive functioning. In particular, greater levels of physical activity offset a deleterious effect of the Met allele on working memory performance. These findings suggest that physical activity can modulate domain-specific genetic (BDNF) effects on cognition." [120]

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Physical exercise improves peripheral BDNF levels and cognitive functions in mild cognitive impairment elderly with different BDNF Val66Met genotypes.

http://www.ncbi.nlm.nih.gov/pubmed/25062900 [121]

"...the objective of this study was to analyze the effects of a multimodal physical exercise program on peripheral BDNF levels and cognitive functions in elderly individuals with mild cognitive impairment (MCI)…The results showed a significant between-subjects interaction ($p < 0.05$), which indicates the beneficial contribution of training on cognitive functions independent of the BDNF genotype. However, only participants with BDNF-Met genotypes exhibited significant improvements in peripheral BDNF levels. The BDNF genotype appears to modulate the effects of physical exercise on BDNF secretion, but it does not influence cognition. This is the first study that evaluated the influence of a BDNF polymorphism on physical activity and cognition performance in elderly MCI individuals." [121]

1.12 Gene Tested: Mu Opioid Receptor (OPRM1)

Pharmacogenetics of OPRM1

http://www.ncbi.nlm.nih.gov/pubmed/24201053/ [122]

"The OPRM1 gene has been a target of interest in a large number of pharmacogenetic studies due to its genetic and structural variation, as well as the role of opioid receptors in a variety of disorders. The mu-opioid receptor (MOR), encoded by OPRM1, naturally regulates the analgesic response to pain and also controls the rewarding effects of many drugs of abuse, including opioids, nicotine, and alcohol. Genetic variants in OPRM1, particularly the non-synonymous polymorphism A118G, have been repeatedly associated with the efficacy of treatments for pain and various types of dependence. This review focuses on the current understanding of the pharmacogenetic impact of OPRM1, primarily with regard to the treatment of pain and addiction." [122]

The impact of genetic variation on sensitivity to opioid analgesics in patients with postoperative pain: a systematic review and meta-analysis.

http://www.ncbi.nlm.nih.gov/pubmed/25794200 [123]

"This study sought to clarify the impact of distinct genetic variations on pain, opioid consumption, and opioid side effects in patients with postoperative pain. The results showed that human μ-opioid receptor gene (OPRM1) 118G allele variant carriers consumed more opioids for analgesia (SMD = -0.17, 95% CI = [-0.25, -0.10], $P < 0.00001$), but reported higher pain scores (MD = -0.11, 95% CI = [-0.17, -0.04], $P = 0.002$) and less nausea and vomiting (odds ratio = 1.30, 95% CI = [1.08, 1.55], $P = 0.005$) than the homozygous 118AA patients during the first 24 hour but not the 48 hour postoperative period…the A118G allele variant of OPRM1 has the most potent influence on pain management of postoperative patients. Opioid receptor gene information may provide valuable information for clinicians to properly manage the analgesic use of opioids individually for better pain management." [123]

Genotyping test with clinical factors: better management of acute postoperative pain?

http://www.ncbi.nlm.nih.gov/pubmed/25809606 [124]

"The aim of this study is to investigate the influence of genetic and non-genetic factors on the variability of response to morphine in acute postoperative pain…OPRM1 and ABCB1 polymorphisms were significantly associated with administered dose of morphine ($p = 0.038$ and 0.012 respectively). Patients with at least one G allele for c.118A>G OPRM1 polymorphism (AG/GG) needed 4 times the dose of morphine of AA patients…Our preliminary results support the evidence that OPRM1/ABCB1 genotypes along with age, weight and duration of operation have an impact on morphine consumption for acute postoperative pain treatment." [124]

OPRM1 rs1799971 polymorphism and opioid dependence: evidence from a meta-analysis

http://www.ncbi.nlm.nih.gov/pubmed/23651028 [125]

"The OPRM1 gene encodes the μ-opioid receptor, which is the primary site of action of most opioids. Several studies and three meta-analyses have examined a possible link between the exonic OPRM1 A118G (rs1799971) polymorphism and opioid dependence; however, results have been inconclusive… Our meta-analysis showed significant association between this polymorphism and susceptibility to opioid dependence in overall studies under a codominant model, as well as susceptibility to opioid dependence or heroin dependence in Asians under an autosomal dominant model. The nonsynonymous OPRM1 rs1799971 might be a risk factor for addiction to opioids or heroin in an Asian population." [125]

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1.13 Gene Tested: Glutamate Receptor Kainate 1 (GRIK1)

Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism.
http://www.ncbi.nlm.nih.gov/pubmed/24525690 [126]

"Topiramate has been shown to reduce drinking and heavy drinking in individuals with alcohol dependence whose goal was to stop drinking. The authors evaluated the efficacy and tolerability of topiramate in heavy drinkers whose treatment goal was to reduce drinking to safe levels... Topiramate treatment significantly reduced heavy drinking days and increased abstinent days relative to placebo..In a European American subsample (N=122), topiramate's effect on heavy drinking days was significantly greater than that for placebo only in rs2832407 C-allele homozygotes. These findings support the use of topiramate at a daily dose of 200 mg to reduce heavy drinking in problem drinkers. The moderator effect of rs2832407, if validated, would facilitate the identification of heavy drinkers who are likely to respond well to topiramate treatment and provide an important personalized treatment option. The pharmacogenetic findings also implicate the kainate receptor in the mechanism of topiramate's effects on heavy drinking." [126]

Posttreatment effects of topiramate treatment for heavy drinking.
http://www.ncbi.nlm.nih.gov/pubmed/25581656[127]

"We examined whether the effects of topiramate and a single nucleotide polymorphism (rs2832407) in GRIK1, which encodes a kainate receptor subunit, persisted following a 12-week, placebo-controlled trial in 138 heavy drinkers with a treatment goal of reduced drinking. During treatment, topiramate 200 mg/d significantly reduced heavy drinking days and increased the frequency of abstinent days (Am J Psychiatry, 2014, 171:445). In the European-American (EA) subsample (n = 122), rs2832407 moderated the treatment effect on heavy drinking. In the full sample, the lower PHDD and higher PDA seen with topiramate treatment were no longer significant during follow-up. Nonetheless, the topiramate-treated patients had lower alcohol-related problem scores during treatment and both follow-up periods. Further, in the EA subsample, the greater reduction in PHDD seen with topiramate treatment in rs2832407 C-allele homozygotes persisted throughout follow-up, with no significant effects in A-allele carriers. A reduction in GGTP concentration was consistent with the reduction in heavy drinking, but did not reach statistical significance." [127]

GRIK1 genotype moderates topiramate's effects on daily drinking level, expectations of alcohol's positive effects and desire to drink.
http://www.ncbi.nlm.nih.gov/pubmed/24786948 [128]

"We found that rs2832407 C allele homozygotes treated with topiramate drank less overall during treatment than those receiving placebo, validating our earlier findings for heavy drinking days (Kranzler et al., 2014). There was also a study day × medication group × genotype group interaction that predicted both positive alcohol expectancies and desire to drink, with rs2832407 C-allele homozygotes treated with topiramate showing the largest decreases in these outcomes during the study period. Changes in positive alcohol expectancies or desire to drink did not mediate the effects on drinking. These findings validate and extend our previous pharmacogenetic findings with topiramate." [128]

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Pharmacokinetic Genes

1.14 Gene Tested: Cytochrome P450 1A2: (CYP1A2)

Pharmacogenetics of second-generation antipsychotics
http://www.ncbi.nlm.nih.gov/pubmed/24897292 [54]

The Human Cytochrome P450 (CYP) Allele Nomenclature Database
http://www.cypalleles.ki.se/ [129]

PharmGKB The Pharmacogenomics Knowledgebase
https://www.pharmgkb.org/ [130]

Clinical applications of CYP genotyping in psychiatry
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [131]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [132]

There is a large amount of variability in psychotropic drug response and variations in CYP450 genes, including CYP1A2, may impact this variability. There are several articles which review the relevant clinical implications of altered CYP1A2 metabolism. [54,129-132]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [133]

"Human liver samples and applied a systems biology approach via the integration of genetics, gene expression, and enzyme activity measurements. We found that most P450s were positively correlated among themselves and were highly correlated with known regulators as well as thousands of other genes enriched for pathways relevant to the metabolism of drugs, fatty acids, amino acids, and steroids. Genome-wide association analyses between genetic polymorphisms and P450 expression or enzyme activities revealed sets of SNPs associated with P450 traits, and suggested the existence of both cis-regulation of P450 expression (especially for CYP2D6) and more complex trans-regulation of P450 activity." [133]

CYP450 pharmacogenetic treatment strategies for antipsychotics: a review of the evidence
http://www.ncbi.nlm.nih.gov/pubmed/23870808 [134]

"CYP2D6, CYP1A2, and CYP3A4/5 are major enzymes in the metabolism of antipsychotics and polymorphisms of alleles for these proteins are associated with altered plasma levels… Numerous studies have shown a significant association between genotype and adverse effects, such as CYP2D6 polymorphisms and tardive dyskinesia. This review summarizes evidence for the role of CYP450 genetic variants in the response to antipsychotic medications and the clinical implications of pharmacogenetics in the management of patients with schizophrenia." [134]

Insights into the substrate specificity, inhibitors, regulation, and polymorphisms and the clinical impact of human cytochrome P450 1A2
http://www.ncbi.nlm.nih.gov/pubmed/19590965 [135]

"To date, more than 15 variant alleles and a series of subvariants of the CYP1A2 gene have been identified and some of they have been associated with altered drug clearance and response to drug therapy. For example, lack of response to clozapine therapy due to low plasma drug levels has been reported in smokers harboring the -163A/A genotype; there is an association between CYP1A2*1F (-163C>A) allele and the risk for leflunomide-induced host toxicity. The *1F allele is associated with increased enzyme inducibility whereas *1C causes reduced inducibility. Further studies are warranted to explore the clinical and toxicological significance of altered CYP1A2 expression and activity caused by genetic, epigenetic, and environmental factors." [135]

CYP1A2 is more variable than previously thought: a genomic biography of the gene behind the human drug-metabolizing enzyme.
http://www.ncbi.nlm.nih.gov/pubmed/20881513 [136]

"As human genetic diversity has been reported to decrease with distance from Ethiopia, we resequenced CYP1A2 in five Ethiopian ethnic groups representing a rough northeast to southwest transect across… We found 49 different variable sites (30 of which are novel), nine nonsynonymous changes (seven of which are novel), one synonymous change and 55 different haplotypes, only three of which are previously reported." [136]

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The Dosing of Atypical Antipsychotics

http://www.ncbi.nlm.nih.gov/pubmed/15883149 [137]

"Dosage alterations of …quetiapine, dependent on cytochrome P450 3A (CYP3A), may be necessary when used with other drugs that inhibit or induce their metabolic enzymes. Genetic variations of cytochrome P450 2D6 (CYP2D6) and drug-drug interactions causing inhibition (CYP2D6 and/or CYP3A) or induction (CYP3A) may be important for risperidone, and perhaps for aripiprazole, dosing. Adding inhibitors may cause side effects more easily in drugs with a narrow therapeutic window, such as clozapine or risperidone, than in those with a wide therapeutic window, such as olanzapine or aripiprazole. Adding inducers may be associated with a gradual development of lost efficacy." [137]

Variation in CYP1A2 activity and its clinical implications: influence of environmental factors and genetic polymorphisms

http://www.ncbi.nlm.nih.gov/pubmed/18466106 [138]

"CYP1A2 is involved in the metabolism of several widely used drugs and endogenous compounds, and in the activation of procarcinogens. Both genetic and environmental factors influence the activity of this enzyme. The current knowledge regarding factors influencing the activity of CYP1A2 is summarized in this review…The functional significance and clinical importance of CYP1A2 gene polymorphisms are reviewed and interethnic differences in the distribution of CYP1A2 variant alleles and haplotypes are summarized. Finally, future perspectives for the possible clinical applications of CYP1A2 genotyping are discussed." [138]

A theoretical study on the mechanism of a superficial mutation inhibiting the enzymatic activity of CYP1A2

http://www.ncbi.nlm.nih.gov/pubmed/24464701 [139]

"CYP1A2, one of the major members of cytochrome P450 in human liver, participates in the metabolism of various drugs. While most harmful mutations are located near the catalytic core of CYP1A2, a recently found loss-of-function mutation, F186L, is on the surface… Based on these findings, a detailed mechanism of how F186 regulates the functions of CYP1A2 was proposed, and it may shed light on the diverse effects of SNPs and the personalized drug design." [139]

Six novel nonsynonymous CYP1A2 gene polymorphisms: catalytic activities of the naturally occurring variant enzymes.

http://www.ncbi.nlm.nih.gov/pubmed/14563787 [140]

"Six novel nonsynonymous nucleotide alterations were found in the cytochrome P450 1A2 gene in a Japanese population, which resulted in the following amino acid substitutions: T83M, E168Q, F186L, S212C, G299A, and T438I…Kinetic analyses performed for the ethoxyresorufin O-deethylation revealed that the Vmax of the F186L (*11) variant was approximately 5% of that of the CYP1A2 wild type, despite a 5-fold lower Km value of the variant, the consequence of which was reduced enzymatic activity toward the substrate. Thus, for the first time, phenylalanine at residue 186 is suggested to be a critical amino acid for catalytic activity." [140]

Association between CYP1A2 polymorphisms and clozapine induced adverse reaction in patients with schizophrenia

http://www.ncbi.nlm.nih.gov/pubmed/22901441 [141]

"CYP1A2 *1F contains a 163 C4A transition in intron 1, which influences the gene inducibility affecting the magnitude of increase of caffeine metabolism after smoking…CYP1A2 alleles *1C, *1D and *1F are all due to mutations in the regulatory regions of the gene and at least for CYP1A2 *1C and *1F, the functional effects associated with their presence have been adequately characterised. CYP1A2 *1C contains a 3860 G>A transition in the flanking region of the gene, causing decrease in its inducibility. CYP1A2 *1F contains a 163 C>A transition in intron 1, which influences the gene inducibility affecting the magnitude of increase of caffeine metabolism after smoking…Patients with ADRs had a higher frequency of CYP1A2 low activity allele combinations (8/12; 67%) and lower CYP1A2-mRNA levels than patients without ADRs (6/22; 27%, P = 0.019)." [141]

Impact of CYP1A2 and CYP2D6 polymorphisms on drug metabolism and on insulin and lipid elevations and insulin resistance in clozapine-treated patients

http://www.ncbi.nlm.nih.gov/pubmed/17503978 [142]

"Clozapine and N-desmethylclozapine concentration-to-dose (C/D) ratios were significantly higher in patients carrying 2 CYP1A2 single nucleotide polymorphisms (SNPs), previously suggested to cause low enzyme activity, compared to those with no such SNPs ($p < .05$)… CYP1A2 variants *1C and *1D seem to be associated with higher serum clozapine concentrations and an increased risk of developing insulin and lipid elevations and insulin resistance on a given dose of clozapine." [142]

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Influence of the genetic polymorphism in the 5'-noncoding region of the CYP1A2 gene on CYP1A2 phenotype and urinary mutagenicity in smokers

http://www.ncbi.nlm.nih.gov/pubmed/16188490 [143]

"The functional significance of genetic polymorphisms on tobacco smoke-induced CYP1A2 activity was examined…Heavy smokers (n=48, with urinary nicotine plus its metabolites>or=0.69 mg/mmol creatinine) with variant allele -2467delT or -163A had significantly increased urinary mutagenicity (p<0.01 and <0.05). CYP1A2 genetic polymorphisms are shown to influence the CYP1A2 phenotype in smokers, -2467 T-->delT having the main effect. This information is of interest for future studies assessing the possible role of tobacco smoke-inducible CYP1A2 genotypes as individual susceptibility factors in exposure to carcinogens." [143]

CYP1A2 genetic polymorphisms are associated with early antidepressant escitalopram metabolism and adverse reactions.

http://www.ncbi.nlm.nih.gov/pubmed/23859573 [144]

"The liver CYP1A2 enzyme may metabolize antidepressant escitalopram (S-CIT) to S-desmethylcitalopram (S-DCIT) and S-didesmethylcitalopram (S-DDCIT). This study tested whether genetic polymorphisms in the CYP1A2 gene are associated with the treatment responses to S-CIT…CYP1A2 SNPs rs2069521, rs2069526, rs4646425 and rs4646427 are significantly associated with the metabolic ratios of S-DDCIT/S-DCIT (p = 0.002, 0.018, 0.008 and 0.004, respectively) at week 2 of treatment. Carriers of the allele types associated with higher S-DDCIT/S-DCIT ratios had more severe side effects…These results suggest that genetic variants in CYP1A2 may be indicators for S-CIT metabolism and that the fast metabolizers may experience more severe adverse reactions in the early stages of S-CIT treatment. Original submitted 27 December 2012; Revision submitted 15 May 2013." [144]

Pharmacogenetics and olanzapine treatment: CYP1A2*1F and serotonergic polymorphisms influence therapeutic outcome.

http://www.ncbi.nlm.nih.gov/pubmed/19636338 [145]

"In our study population, CYP1A2*1F/*1F genotype alone resulted in a 22% reduction of dose-/body weight-normalized olanzapine serum concentrations compared to homo- and heterozygote carriers of CYP1A2*1A (both groups without inducers). This effect was independent of the well-known effect of inducing agents (here tobacco smoke and carbamazepine which led to on average 28% lower concentrations in CYP1A2*1A carriers and 26% lower concentrations in CYP1A2*1F/*1F carriers). Consistently, patients with the CYP1A2*1F/*1F genotype taking inducers had 22% lower concentrations compared to CYP1A2*1A carriers taking inducers. The influence of genotype alone remained significant after Bonferroni's post hoc test." [145]

Genetics of caffeine consumption and responses to caffeine

http://www.ncbi.nlm.nih.gov/pubmed/20532872 [146]

"Modeling based on twin studies reveals that genetics plays a role in individual variability in caffeine consumption and in the direct effects of caffeine. Both pharmacodynamic and pharmacokinetic polymorphisms have been linked to variation in response to caffeine… A single nucleotide C→A polymorphism at position 734 within intron 1 (rs762551) is correlated with high inducibility of the P-450 1A2 enzyme in Caucasian subjects (Sachse et al. 1999). Smoking subjects with A/A genotype metabolize caffeine at 1.6 times the rate of the other genotypes, while no significant differences are found for nonsmoking subjects. The genetic polymorphism therefore modifies environmental impact on enzyme activity." [146]

Inducibility of CYP1A2 by omeprazole in vivo related to the genetic polymorphism of CYP1A2

http://www.ncbi.nlm.nih.gov/pubmed/12445035 [147]

"Mutations of CYP2C19 and CYP1A2 were identified by PCR-RFLP. Omeprazole, 120 mg day-1, was given to 12 extensive metabolizers (EM) with respect to CYP2C19 (six CYP1A2*1F/CYP1A2*1F and six CYP1A2*1C/CYP1A2*1F of CYP1A2) for 7 days. CYP1A2 activity was determined on three occasions, namely on day 1, day 9 and day 16 using the caffeine plasma index (the ratio of the concentrations of paraxanthine to caffeine), 6 h after oral administration of 200 mg caffeine… There was a significant difference (P = 0.002) between the caffeine ratios for CYP1A2*1F/CYP1A2*1F and CYP1A2*1C/CYP1A2*1F genotypes on day 9, but not on day 1 or day 16 (P > 0.05). The changes in the ratios from day 9 to day 1 (48% +/- 20%vs 19% +/- 20%) and from day 9 to day 16 (50% +/- 31%vs 15% +/- 22%) were significantly different (P < 0.05) between the CYP1A2*1F/CYP1A2*1F and CYP1A2*1C/CYP1A2*1F genotypes… The CYP1A2*1C and CYP1A2*1F genetic polymorphisms influenced the induction of CYP1A2 activity in vivo by omeprazole." [147]

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CYP1A2, GSTM1, and GSTT1 polymorphisms and diet effects on CYP1A2 activity in a crossover feeding trial.
http://www.ncbi.nlm.nih.gov/pubmed/19843669 [148]

"Using a randomized, crossover feeding trial in humans, we investigated the dose effects of cruciferous vegetables and the effects of any interaction between cruciferous and apiaceous vegetables on CYP1A2 activity. We also investigated whether response varied by CYP1A2*1F, GSTM1, and GSTT1 genotypes (glutathione S-transferases that metabolize crucifer constituents) and whether CYP1A2 activity rebounds after apiaceous vegetables are removed from the diet…These results suggest complex interactions among dietary patterns, genetic variation, and modulation of biotransformation that may not be apparent in observational studies." [148]

Duloxetine: clinical pharmacokinetics and drug interactions
http://www.ncbi.nlm.nih.gov/pubmed/21366359 [149]

"Patient demographic characteristics found to influence the pharmacokinetics of duloxetine include sex, smoking status, age, ethnicity, cytochrome P450 (CYP) 2D6 genotype, hepatic function and renal function… Pharmacokinetic results from drug interaction studies show that activated charcoal decreases duloxetine exposure, and that CYP1A2 inhibition increases duloxetine exposure to a clinically significant degree… Specifically, following oral administration in the presence of fluvoxamine, the area under the plasma concentration-time curve and C(max) ofduloxetine significantly increased by 460% (90% CI 359, 584) and 141% (90% CI 93, 200), respectively. In addition, smoking is associated with a 30% decrease in duloxetine concentration. The exposure of duloxetine with CYP2D6 inhibitors or in CYP2D6 poor metabolizers is increased to a lesser extent than that observed with CYP1A2 inhibition and does not require a dose adjustment." [149]

1.15 Gene Tested: Cytochrome P450 2B6: (CYP2B6)

The Human Cytochrome P450 (CYP) Allele Nomenclature Database
http://www.cypalleles.ki.se/ [129]

PharmGKB The Pharmacogenomics Knowledgebase
https://www.pharmgkb.org/ [130]

Clinical applications of CYP genotyping in psychiatry
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [131]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [132]

Applications of CYP450 testing in the clinical setting
http://www.ncbi.nlm.nih.gov/pubmed/23588782 [150]

There is a large amount of variability in psychotropic drug response and variations in CYP450 genes, including CYP2B6, may impact this variability. There are several articles which review the relevant clinical implications of altered CYP2B6 metabolism. [129-132,150]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [133]

"Human liver samples and applied a systems biology approach via the integration of genetics, gene expression, and enzyme activity measurements. We found that most P450s were positively correlated among themselves and were highly correlated with known regulators as well as thousands of other genes enriched for pathways relevant to the metabolism of drugs, fatty acids, amino acids, and steroids. Genome-wide association analyses between genetic polymorphisms and P450 expression or enzyme activities revealed sets of SNPs associated with P450 traits, and suggested the existence of both cis-regulation of P450 expression (especially for CYP2D6) and more complex trans-regulation of P450 activity." [133]

Pharmacogenetics of cytochrome P450 2B6 (CYP2B6): advances on polymorphisms, mechanisms, and clinical relevance
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3588594/ [151]

CYP2B6: New Insights into a Historically Overlooked Cytochrome P450 Isozyme
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2605793/ [152]

CYP2B6 is responsible for the metabolism of several medications including bupropion and methadone. This gene is also displays highly variable expression between individuals due to genetic variation, environmental contributions, and inhibition and induction effects of other co-administered medications and food products. Resent advances in the understanding of this enzyme have made it a potential therapeutic target. [151,152]

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Prevalence of poor and rapid metabolizers of drugs metabolized by CYP2B6 in North Indian population residing in Indian national capital territory

http://www.ncbi.nlm.nih.gov/pubmed/23961363 [153]

"Identification of poor and rapid metabolizers for the category of drugs metabolized by cytochrome P450 2B6 (CYP2B6) is important for understanding the differences in clinical responses of drugs metabolized by this enzyme... Results indicate that 20.56% individuals in the target population were poor metabolizers for the category of drugs metabolized by CYP2B6. The baseline information would be clinically useful before administering the drugs metabolized by this isoform." [153]

Polymorphic Variants of Cytochrome P450 2B6 (CYP2B6.4–CYP2B6.9) Exhibit Altered Rates of Metabolism for Bupropion and Efavirenz: A Charge-Reversal Mutation in the K139E Variant (CYP2B6.8) Impairs Formation of a Functional Cytochrome P450-Reductase Complex

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3164347/ [154]

"In this study, metabolism of bupropion, efavirenz, and 7-ethoxy-4-trifluoromethylcoumarin (7-EFC) by CYP2B6 wild type (CYP2B6.1) and six polymorphic variants (CYP2B6.4 to CYP2B6.9) was investigated in a reconstituted system to gain a better understanding of the effects of the mutations on the catalytic properties of these naturally occurring variants… In this work, we have characterized the catalytic properties of six polymorphic variants of CYP2B6 (CYP2B6.4 to CYP2B6.9) in a reconstituted system to gain a better understanding of the mechanism by which these genetic mutations affect the catalytic activities of CYP2B6… Results from this work provide further insights to better understand the genotype–phenotype correlation regarding CYP2B6 polymorphisms and drug metabolism." [154]

Extensive genetic polymorphism in the human CYP2B6 gene with impact on expression and function in human liver.

http://www.ncbi.nlm.nih.gov/pubmed/11470993 [155]

"In this study, we present the first systematic investigation of genetic polymorphism in the CYP2B6 gene on chromosome 19… A total of nine novel point mutations were identified, of which five result in amino acid substitutions in exon 1 (C64T, Arg22Cys), exon 4 (G516T, Gln172His), exon 5 (C777A, Ser259Arg and A785G, Lys262Arg) and exon 9 (C1459T, Arg487Cys) and four are silent mutations (C78T, G216C, G714A and C732T)… By screening a population of 215 subjects the C64T, G516T, C777A, A785G and C1459T mutations were found at frequencies of 5.3%, 28.6%, 0.5%, 32.6% and 14.0%, respectively. Haplotype analysis revealed six different mutant alleles termed CYP2B6*2 (C64T), *3 (C777A), *4 (A785G), *5 (C1459T), *6 (G516T and A785G) and *7 (G516T, A785G and C1459T). By analysing a large number of human liver samples, significantly reduced CYP2B6 protein expression and S-mephenytoin N-demethylase activity were found in carriers of the C1459T (R487C) mutation (alleles *5 and *7). These data demonstrate that the extensive interindividual variability of CYP2B6 expression and function is not only due to regulatory phenomena, but also caused by a common genetic polymorphism." [155]

Aberrant splicing caused by single nucleotide polymorphism c.516G>T [Q172H], a marker of CYP2B6*6, is responsible for decreased expression and activity of CYP2B6 in liver.

http://www.ncbi.nlm.nih.gov/pubmed/18171905 [156]

"The common allele CYP2B6*6 [c. 516G>T, Q172H, and c.785A>G, K262R] has previously been associated with lower expression in human liver and with increased plasma levels of efavirenz in human immunodeficiency virus patients, but the molecular mechanism has remained unclear. We present novel data showing that hepatic CYP2B6 mRNA levels are reduced in *6 carriers, suggesting a pretranslational mechanism resulting in decreased expression." [156]

Impact of CYP2B6 polymorphism on hepatic efavirenz metabolism in vitro.

http://www.ncbi.nlm.nih.gov/pubmed/17559344 [157]

"We have shown that CYP2B6 genetic polymorphism markedly influences the metabolism of efavirenz in human liver microsomes. Importantly, the CYP2B6*6 allele harboring the SNPs c.516G>T [Q172H] and c.785A>G [K262R] was significantly associated with a pronounced decrease in CYP2B6 expression and activity, as well as a low rate of efavirenz 8-hydroxylation. These results represent a first step towards elucidating the mechanism by which this allele identifies patients exhibiting very high efavirenz plasma concentrations." [157]

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CYP2B6 SNPs are associated with methadone dose required for effective treatment of opioid addiction.
http://www.ncbi.nlm.nih.gov/pubmed/21790905 [158]

"Adequate methadone dosing in methadone maintenance treatment (MMT) for opioid addiction is critical for therapeutic success. One of the challenges in dose determination is the inter-individual variability in dose-response. Methadone metabolism is attributed primarily to cytochrome P450 enzymes CYP3A4, CYP2B6 and CYP2D6. The CYP2B6*6 allele [single nucleotide polymorphisms (SNPs) 785A>G (rs2279343) and 516G>T (rs3745274)] was associated with slow methadone metabolism… The results remain significant after controlling for age, sex and the ABCB1 SNP 1236C>T (rs1128503), which was previously shown to be associated with high methadone dose requirement in this population (P=0.006, 0.030, respectively). An additional 77 CYP2B6, CYP3A4 and CYP2D6 SNPs were genotyped. Of these, 24 SNPs were polymorphic and none showed significant association with methadone dose. Further studies are necessary to replicate these preliminary findings in additional subjects and other populations." [158]

1.16 Gene Tested: Cytochrome P450 2C9: (CYP2C9)

The Human Cytochrome P450 (CYP) Allele Nomenclature Database
http://www.cypalleles.ki.se/ [129]

PharmGKB The Pharmacogenomics Knowledgebase
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Clinical applications of CYP genotyping in psychiatry
http://www.ncbi.nlm.nih.gov/pubmed/252005855 [131]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [132]

Applications of CYP450 testing in the clinical setting
http://www.ncbi.nlm.nih.gov/pubmed/23588782 [150]

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Cytochrome P450 2C9-CYP2C9.
http://www.ncbi.nlm.nih.gov/pubmed/20150829 [159]

"CYP2C9 is a phase I drug-metabolizing cytochrome P450 (CYP450) enzyme isoform that plays a major role in the oxidation of both xenobiotic and endogenous compounds… CYP2C9 is a phase I drug-metabolizing cytochrome P450 (CYP450) enzyme isoform that plays a major role in the oxidation of both xenobiotic and endogenous compounds." [159]

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Pharmacogenetics: From Bench to Byte— An Update of Guidelines
http://www.ncbi.nlm.nih.gov/pubmed/21412232 [160]

"Currently, there are very few guidelines linking the results of pharmacogenetic tests to specific therapeutic recommendations... After systematic review of the literature, recommendations were developed for 53 drugs associated with genes coding for CYP2D6, CYP2C19, CYP2C9, thiopurine-S-methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPD), vitamin K epoxide reductase (VKORC1), uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), HLA-B44, HLA-B*5701, CYP3A5, and factor V Leiden (FVL)." [160]

Characterization of 107 Genomic DNA Reference Materials for *CYP2D6*, *CYP2C19*, *CYP2C9*, *VKORC1*, and *UGT1A1*
http://www.ncbi.nlm.nih.gov/pubmed/20889555 [161]

"[T]he Centers for Disease Control and Prevention's Genetic Testing Reference Material Coordination Program, in collaboration with members of the pharmacogenetics testing community and the Coriell Cell Repositories, have characterized a panel of 107 genomic DNA reference materials for five loci (*CYP2D6*, *CYP2C19*, *CYP2C9*, *VKORC1*, and *UGT1A1*) that are commonly included in pharmacogenetic testing panels and proficiency testing surveys. Genomic DNA from publicly available cell lines was sent to volunteer laboratories for genotyping. Each sample was tested in three to six laboratories using a variety of commercially available or laboratory-developed platforms. The results were consistent among laboratories, with differences in allele assignments largely related to the manufacturer's assay design and variable nomenclature, especially for *CYP2D6*. The alleles included in the assay platforms varied, but most were identified in the set of 107 DNA samples." [161]

Drug metabolizing enzyme activities versus genetic variances for drug of clinical pharmacogenomic relevance
http://www.ncbi.nlm.nih.gov/pubmed/21906384 [162]

"Regarding drug metabolism, specific polymorphisms to the cytochrome (CYP) P450 enzyme family are linked to phenotypes that describe reaction rates as "ultra", "intermediate", and "poor," as referenced to "extensive" metabolizers that are assigned to wildtype individuals. Activity scores is an alternate designation that provides more genotype-to-phenotype resolution. Understanding the relative change in enzyme activities or rate of clearance of specific drugs relative to an individual's genotypes is an important component in the interpretation of pharmacogenomic data for personalized medicine." [162]

Polymorphisms of human cytochrome P450 2C9 and the functional relevance.
http://www.ncbi.nlm.nih.gov/pubmed/19715737 [163]

"Human cytochrome P450 2C9 (CYP2C9) accounts for ~20% of hepatic total CYP content and metabolizes ~15% clinical drugs such as phenytoin, S-warfarin, tolbutamide, losartan, and many nonsteroidal anti-inflammatory agents (NSAIDs). CYP2C9 is highly polymorphic, with at least 33 variants of CYP2C9 (*1B through *34) being identified so far… The CYP2C9 polymorphisms are relevant for the efficacy and adverse effects of numerous NSAIDs, sulfonylurea antidiabetic drugs and, most critically, oral anticoagulants belonging to the class of vitamin K epoxide reductase inhibitors… Genetic testing of CYP2C9 is expected to play a role in predicting drug clearance and conducting individualized pharmacotherapy." [163]

CYP2C9*3 Loss-of-Function Allele Is Associated With Acute Upper Gastrointestinal Bleeding Related to the Use of NSAIDs Other Than Aspirin.
http://www.ncbi.nlm.nih.gov/pubmed/20445534 [164]

"Nonsteroidal anti-inflammatory drugs (NSAIDs), other than aspirin, are to some extent metabolized by cytochrome P450 2C9 (CYP2C9). The CYP2C9 359Leu (CYP2C9*3) loss-of-function allele could be a risk factor for acute upper gastrointestinal bleeding (AUGIB) related to the use of NSAIDs other than aspirin. To test this hypothesis, we performed a prospective, multicenter, case-case study in patients hospitalized for AUGIB related to the use of NSAIDs… the results of the study support the hypothesis that the CYP2C9 359Leu allele is a robust risk factor for AUGIB related to the use of NSAIDs other than aspirin." [164]

Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing.
http://www.ncbi.nlm.nih.gov/pubmed/21900891 [165]

"Warfarin is a widely used anticoagulant with a narrow therapeutic index and large interpatient variability in the dose required to achieve target anticoagulation. Common genetic variants in the cytochrome P450-2C9 (CYP2C9) and vitamin K-epoxide reductase complex (VKORC1) enzymes, in addition to known nongenetic factors, account for ~50% of warfarin dose variability." [165]

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Genetically based impairment in CYP2C8- and CYP2C9-dependent NSAID metabolism as a risk factor for gastrointestinal bleeding: is a combination of pharmacogenomics and metabolomics required to improve personalized medicine?
http://www.ncbi.nlm.nih.gov/pubmed/19422321 [166]

"Polymorphisms in CYP2C8 and CYP2C9 are common in all the human populations and many CYP2C8 and CYP2C9 gene variations cause decreased enzyme activity towards the NSAIDs aceclofenac, celecoxib, diclofenac, ibuprofen, indomethazine, lornoxicam, meloxicam, naproxen, piroxicam, tenoxicam and valdecoxib… Individuals carrying the gene variants CYP2C8*3 (rs11572080; rs10509681), CYP2C9*2 (rs1799853) or CYP2C9*3 (rs1057910) show increased risk of developing acute gastrointestinal bleeding during the use of NSAID that are CYP2C8 or CYP2C9 substrates… We present an overview of the current knowledge of relevant polymorphisms of CYP2C8 and CYP2C9 genes, their association with NSAID metabolism and pharmacokinetics and a meta-analysis that confirms the clinical significance of these gene variations with regard to gastrointestinal bleeding." [166]

Decreased warfarin clearance associated with the CYP2C9 R150H (*8) polymorphism.
http://www.ncbi.nlm.nih.gov/pubmed/22378156 [167]

"The cytochrome P450 (CYP) 2C9 R150H (*8) allele occurs commonly in African Americans and is associated with lower warfarin dose requirements… We observed a 30% reduction in the unbound oral clearance of S-warfarin and a 25% lower R- to S-warfarin plasma concentration ratio in patients with the CYP2C9*8 allele (n = 12) as compared to CYP2C9*1 homozygotes (n = 26). Consistent with these findings, the in vitro intrinsic clearance of S-warfarin was 30% lower with the cDNA-expressed R150H protein as compared to the wild-type protein. These data show that the R150H variant protein expressed by the CYP2C9*8 allele is associated with lower S-warfarin clearance." [167]

Role of CYP2C9 and its variants (CYP2C9*3 and CYP2C9*13) in the metabolism of lornoxicam in humans.
http://www.ncbi.nlm.nih.gov/pubmed/15764711[168]

"CYP2C9 is an important member of the cytochrome P450 enzyme superfamily with some 12 CYP2C9 alleles (*1-*12) being previously reported… Mean values of Km and Vmax for CYP2C9*1, *3, and *13 were 1.24, 1.61, and 2.79 microM and 0.83, 0.28, and 0.22 pmol/min/pmol, respectively. Intrinsic clearance values (Vmax/Km) for variant CYP2C9*3 and CYP2C9*13 on the basis of CYP2C9 protein levels were separately decreased to 28% and 12% compared with wild type. In a subsequent clinical study, the AUC of lornoxicam was increased by 1.9-fold and its oral clearance (CL/F) decreased by 44% in three CYP2C9*1/*13 subjects, compared with CYP2C9*1/*1 individuals. This suggests that the CYP2C9*13 allele is associated with decreased enzymatic activity both in vitro and in vivo." [168]

1.17 Gene Tested: Cytochrome P450 2C19: (CYP2C19)

Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy
http://www.ncbi.nlm.nih.gov/pubmed/24151799 [7]

The Human Cytochrome P450 (CYP) Allele Nomenclature Database
http://www.cypalleles.ki.se/ [129]

PharmGKB The Pharmacogenomics Knowledgebase
https://www.pharmgkb.org/ [130]

Clinical applications of CYP genotyping in psychiatry
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [131]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [132]

Applications of CYP450 testing in the clinical setting
http://www.ncbi.nlm.nih.gov/pubmed/23588782 [150]

There is a large amount of variability in psychotropic drug response and variations in CYP450 genes, including CYP2C19, may impact this variability. There are several articles which review the relevant clinical implications of altered CYP2C19 metabolism and also review practice guidelines based upon patients' altered 2C19 metabolic capacity. [7,129-132,150]

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Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [133]

"Human liver samples and applied a systems biology approach via the integration of genetics, gene expression, and enzyme activity measurements. We found that most P450s were positively correlated among themselves and were highly correlated with known regulators as well as thousands of other genes enriched for pathways relevant to the metabolism of drugs, fatty acids, amino acids, and steroids. Genome-wide association analyses between genetic polymorphisms and P450 expression or enzyme activities revealed sets of SNPs associated with P450 traits, and suggested the existence of both cis-regulation of P450 expression (especially for CYP2D6) and more complex trans-regulation of P450 activity." [133]

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors
http://www.ncbi.nlm.nih.gov/pubmed/25974703 [169]

"Selective serotonin reuptake inhibitors (SSRIs) are primary treatment options for major depressive and anxiety disorders. CYP2D6 and CYP2C19 polymorphisms can influence the metabolism of SSRIs, thereby affecting drug efficacy and safety. We summarize evidence from the published literature supporting these associations and provide dosing recommendations for fluvoxamine, paroxetine, citalopram, escitalopram, and sertraline based on CYP2D6 and/or CYP2C19 genotype (updates at www.pharmgkb.org)." [169]

Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants
http://www.ncbi.nlm.nih.gov/pubmed/23486447 [170]

"Polymorphisms in CYP2D6 and CYP2C19 affect the efficacy and safety of tricyclics, with some drugs being affected by CYP2D6 only, and others by both polymorphic enzymes. Amitriptyline, clomipramine, doxepin, imipramine, and trimipramine are demethylated by CYP2C19 to pharmacologically active metabolites. These drugs and their metabolites, along with desipramine and nortriptyline, undergo hydroxylation by CYP2D6 to less active metabolites. Evidence from published literature is presented for CYP2D6 and CYP2C19 genotype-directed dosing of tricyclic antidepressants." [170]

Pharmacogenetics: From Bench to Byte— An Update of Guidelines
http://www.ncbi.nlm.nih.gov/pubmed/21412232 [160]

"Currently, there are very few guidelines linking the results of pharmacogenetic tests to specific therapeutic recommendations... After systematic review of the literature, recommendations were developed for 53 drugs associated with genes coding for CYP2D6, CYP2C19, CYP2C9, thiopurine-S-methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPD), vitamin K epoxide reductase (VKORC1), uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), HLA-B44, HLA-B*5701, CYP3A5, and factor V Leiden (FVL)." [160]

Characterization of 107 Genomic DNA Reference Materials for *CYP2D6*, *CYP2C19*, *CYP2C9*, *VKORC1*, and *UGT1A1*
http://www.ncbi.nlm.nih.gov/pubmed/20889555 [161]

"[T]he Centers for Disease Control and Prevention's Genetic Testing Reference Material Coordination Program, in collaboration with members of the pharmacogenetics testing community and the Coriell Cell Repositories, have characterized a panel of 107 genomic DNA reference materials for five loci (*CYP2D6*, *CYP2C19*, *CYP2C9*, *VKORC1*, and *UGT1A1*) that are commonly included in pharmacogenetic testing panels and proficiency testing surveys. Genomic DNA from publicly available cell lines was sent to volunteer laboratories for genotyping. Each sample was tested in three to six laboratories using a variety of commercially available or laboratory-developed platforms. The results were consistent among laboratories, with differences in allele assignments largely related to the manufacturer's assay design and variable nomenclature, especially for *CYP2D6*. The alleles included in the assay platforms varied, but most were identified in the set of 107 DNA samples." [161]

Drug metabolizing enzyme activities versus genetic variances for drug of clinical pharmacogenomic relevance
http://www.ncbi.nlm.nih.gov/pubmed/21906384 [162]

"Regarding drug metabolism, specific polymorphisms to the cytochrome (CYP) P450 enzyme family are linked to phenotypes that describe reaction rates as "ultra", "intermediate", and "poor," as referenced to "extensive" metabolizers that are assigned to wildtype individuals. Activity scores is an alternate designation that provides more genotype-to-phenotype resolution. Understanding the relative change in enzyme activities or rate of clearance of specific drugs relative to an individual's genotypes is an important component in the interpretation of pharmacogenomic data for personalized medicine." [162]

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Metabolic ratios of psychotropics as indication of cytochrome P450 2D6/2C19 genotype

http://www.ncbi.nlm.nih.gov/pubmed/16044105 [171]

"The relationships between the observed metabolic ratios and CYP2D6 and/or CYP2C19 genotype were characterized using nonparametric statistical analysis… According to these data, correlations exist between the log(MR) of venlafaxine, amitriptyline, and risperidone and the genotype of the CYP enzymes involved in their metabolism. From the ranges of log(MR) defined here, a high percentage of aberrant metabolizers can be detected even when patients are not routinely genotyped. Thus, the metabolic ratio may serve as an indication of when genotyping should be considered." [171]

CYP2C19 variation and citalopram response

http://www.ncbi.nlm.nih.gov/pubmed/21192344 [172]

"CYP2C19 and CYP3A4 play a primary role in citalopram metabolism, whereas CYP2D6 plays a secondary role… Generally, patients who had CYP2C19 genotypes associated with decreased metabolism were less likely to tolerate citalopram than those with increased metabolism, although this difference was not statistically significant (P = 0.06). However, patients with the inactive 2C19*2 allele had significantly lower odds of tolerance (P = 0.02)… this study showed that variations in CYP2C19 were associated with tolerance and remission in a large sample of White non-Hispanic patients treated with citalopram." [172]

Impact of the Ultrarapid CYP2C19*17 Allele on Serum Concentration of Escitalopram in Psychiatric Patients

http://www.ncbi.nlm.nih.gov/pubmed/17625515 [173]

The CYP2C19*17 genotype is associated with lower imipramine plasma concentrations in a large group of depressed patients

http://www.ncbi.nlm.nih.gov/pubmed/19884907 [174]

CYP2C19*17 affects R-warfarin plasma clearance and warfarin INR/dose ratio in patients on stable warfarin maintenance therapy

http://www.ncbi.nlm.nih.gov/pubmed/25652102 [175]

Cytochrome 2C19*17 Allelic Variant, Platelet Aggregation, Bleeding Events, and Stent Thrombosis in Clopidogrel-Treated Patients With Coronary Stent Placement

http://www.ncbi.nlm.nih.gov/pubmed/20083681 [176]

A recently explored CYP2C19*17 allelic variant has been linked to increased transcriptional activity, resulting in increased metabolism of CYP2C19 substrates. The *17 allele leads to ultrarapid metabolism of CYP2C19 substrates, producing lower plasma levels of drugs and probable decreases in efficacy. [173-176]

Influence of CYP2D6 and CYP2C19 genotypes on venlafaxine metabolic ratios and stereoselective metabolism in forensic autopsy cases

http://www.ncbi.nlm.nih.gov/pubmed/25245581 [177]

"We investigated whether polymorphisms in the CYP2D6 and CYP2C19 genes influence the metabolic ratios and enantiomeric S/R ratios of venlafaxine (VEN) and its metabolites O-desmethylvenlafaxine (ODV), N-desmethylvenlafaxine (NDV) and N,O-didesmethylvenlafaxine (DDV) in blood from forensic autopsy cases…Our results show that the CYP2D6 genotype influences the O-demethylation whereas CYP2C19 influences the N-demethylation of VEN and its metabolites. In addition, we show a stereoselective metabolism where CYP2D6 favours the R-enantiomer whereas CYP2C19 favours the S-enantiomer." [177]

Functional characterization of 21 CYP2C19 allelic variants for clopidogrel 2-oxidation

http://www.ncbi.nlm.nih.gov/pubmed/25001882 [178]

"Genetic variations in cytochrome P450 2C19 (CYP2C19) contribute to interindividual variability in the metabolism of therapeutic agents such as clopidogrel… This study evaluated the in vitro oxidation of clopidogrel by 21 CYP2C19 variants harboring amino acid substitutions… Among the 21 CYP2C19 variants, 12 (that is, CYP2C19.5A, CYP2C19.5B, CYP2C19.6, CYP2C19.8, CYP2C19.9, CYP2C19.10, CYP2C19.14, CYP2C19.16, CYP2C19.19, CYP2C19.22, CYP2C19.24 and CYP2C19.25) showed no or markedly low activity compared with the wild-type protein CYP2C19.1B. This comprehensive in vitro assessment provided insights into the specific metabolic activities of CYP2C19 proteins encoded by variant alleles, and this may to be valuable when interpreting the results of in vivo studies." [178]

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Evaluation of the effects of 20 nonsynonymous single nucleotide polymorphisms of CYP2C19 on S-mephenytoin 4'-hydroxylation and omeprazole 5'-hydroxylation
http://www.ncbi.nlm.nih.gov/pubmed/?21325430 [179]

"CYP2C19 is a highly polymorphic enzyme that affects the metabolism of a wide range of therapeutic drugs…The objective of this study was to functionally characterize 20 nsSNPs of CYP2C19, distributed throughout the entire coding region, most of which have not been thoroughly characterized… CYP2C19.5B, CYP2C19.6, and CYP2C19.8 were found to be catalytically inactive…CYP2C19.9, CYP2C19.10, CYP2C19.16, CYP2C19.18, CYP2C19.19, A161P, W212C, and D360N were substantially altered in catalytic properties in comparison with the WT, with each of these variants exhibiting either dramatically decreased catalytic activities or higher K(m) values." [179]

1.18 Gene Tested: Cytochrome P450 2D6: (CYP2D6)

Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy
http://www.ncbi.nlm.nih.gov/pubmed/24151799 [7]
Pharmacogenetics of second-generation antipsychotics
http://www.ncbi.nlm.nih.gov/pubmed/24897292 [54]
The Human Cytochrome P450 (CYP) Allele Nomenclature Database
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Clinical applications of CYP genotyping in psychiatry
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Applications of CYP450 testing in the clinical setting
http://www.ncbi.nlm.nih.gov/pubmed/23588782 [150]
Polymorphism of Human Cytochrome P450 2D6 and Its Clinical Significance: Part I
http://www.ncbi.nlm.nih.gov/pubmed/19817501 [180]
Polymorphism of Human Cytochrome P450 2D6 and Its Clinical Significance: Part II
http://www.ncbi.nlm.nih.gov/pubmed/19902987 [181]
Recent examples on the clinical relevance of the CYP2D6 polymorphism and endogenous functionality of CYP2D6
http://www.ncbi.nlm.nih.gov/pubmed/24088607 [182]
Pharmacokinetics of Venlafaxine Extended Release 75 mg and Desvenlafaxine 50 mg in Healthy CYP2D6 Extensive and Poor Metabolizers: A Randomized, Open-Label, Two-Period, Parallel-Group, Crossover Study
http://www.ncbi.nlm.nih.gov/pubmed/21288052 [183]
The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation
http://www.ncbi.nlm.nih.gov/pubmed/15669884 [184]

There are numerous studies which support the fact that CYP2D6 metabolizer status can lead to altered drug clearance and levels of active metabolites of psychiatric medications. These changes may lead to increased risk for side effects or treatment inefficacy. For example, CYP2D6 poor metabolizer genotype is associated with increased risk for side effects and medication discontinuation. [7,54,129-132,150,180-184]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [133]

"…we genotyped, expression-profiled, and measured P450 activities of 466 human liver samples and applied a systems biology approach via the integration of genetics, gene expression, and enzyme activity measurements. We found that most P450s were positively correlated among themselves and were highly correlated with known regulators as well as thousands of other genes enriched for pathways relevant to the metabolism of drugs, fatty acids, amino acids, and steroids. Genome-wide association analyses between genetic polymorphisms and P450 expression or enzyme activities revealed sets of SNPs associated with P450 traits, and suggested the existence of both cis-regulation of P450 expression (especially for CYP2D6) and more complex trans-regulation of P450 activity." [133]

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CYP450 pharmacogenetic treatment strategies for antipsychotics: a review of the evidence
http://www.ncbi.nlm.nih.gov/pubmed/23870808 [134]

"CYP2D6, CYP1A2, and CYP3A4/5 are major enzymes in the metabolism of antipsychotics and polymorphisms of alleles for these proteins are associated with altered plasma levels… Numerous studies have shown a significant association between genotype and adverse effects, such as CYP2D6 polymorphisms and tardive dyskinesia. This review summarizes evidence for the role of CYP450 genetic variants in the response to antipsychotic medications and the clinical implications of pharmacogenetics in the management of patients with schizophrenia." [134]

The Dosing of Atypical Antipsychotics
http://www.ncbi.nlm.nih.gov/pubmed/15883149 [137]

"Drug-drug interactions or genetic variability may require using doses different from those recommended for atypical antipsychotics… Genetic variations of cytochrome P450 2D6 (CYP2D6) and drug-drug interactions causing inhibition (CYP2D6 and/or CYP3A) or induction (CYP3A) may be important for risperidone, and perhaps for aripiprazole, dosing. Adding inhibitors may cause side effects more easily in drugs with a narrow therapeutic window, such as clozapine or risperidone, than in those with a wide therapeutic window, such as olanzapine or aripiprazole. Adding inducers may be associated with a gradual development of lost efficacy." [137]

Pharmacogenetics: From Bench to Byte— An Update of Guidelines
http://www.ncbi.nlm.nih.gov/pubmed/21412232 [160]

"[T]he Royal Dutch Association for the Advancement of Pharmacy established the Pharmacogenetics Working Group with the objective of developing pharmacogenetics-based therapeutic (dose) recommendations. After systematic review of the literature, recommendations were developed for 53 drugs associated with genes coding for CYP2D6, CYP2C19, CYP2C9, thiopurine-S-methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPD), vitamin K epoxide reductase (VKORC1), uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), HLA-B44, HLA-B*5701, CYP3A5, and factor V Leiden (FVL)." [160]

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (CYP2D6) genotype
http://www.ncbi.nlm.nih.gov/pubmed/22205192 [185]

"Codeine is bioactivated to morphine, a strong opioid agonist, by the hepatic cytochrome P450 2D6 (CYP2D6); hence, the efficacy and safety of codeine as an analgesic are governed by CYP2D6 polymorphisms. Codeine has little therapeutic effect in patients who are CYP2D6 poor metabolizers, whereas the risk of morphine toxicity is higher in ultrarapid metabolizers. The purpose of this guideline (periodically updated at http://www.pharmgkb.org) is to provide information relating to the interpretation of CYP2D6 genotype test results to guide the dosing of codeine." [185]

Characterization of 107 Genomic DNA Reference Materials for *CYP2D6*, *CYP2C19*, *CYP2C9*, *VKORC1*, and *UGT1A1*
http://www.ncbi.nlm.nih.gov/pubmed/20889555 [161]

"[T]he Centers for Disease Control and Prevention's Genetic Testing Reference Material Coordination Program, in collaboration with members of the pharmacogenetics testing community and the Coriell Cell Repositories, have characterized a panel of 107 genomic DNA reference materials for five loci (*CYP2D6*, *CYP2C19*, *CYP2C9*, *VKORC1*, and *UGT1A1*) that are commonly included in pharmacogenetic testing panels and proficiency testing surveys. Genomic DNA from publicly available cell lines was sent to volunteer laboratories for genotyping. Each sample was tested in three to six laboratories using a variety of commercially available or laboratory-developed platforms. The results were consistent among laboratories, with differences in allele assignments largely related to the manufacturer's assay design and variable nomenclature, especially for *CYP2D6*. The alleles included in the assay platforms varied, but most were identified in the set of 107 DNA samples." [161]

Drug metabolizing enzyme activities versus genetic variances for drug of clinical pharmacogenomic relevance
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"Regarding drug metabolism, specific polymorphisms to the cytochrome (CYP) P450 enzyme family are linked to phenotypes that describe reaction rates as "ultra", "intermediate", and "poor," as referenced to "extensive" metabolizers that are assigned to wildtype individuals. Activity scores is an alternate designation that provides more genotype-to-phenotype resolution. Understanding the relative change in enzyme activities or rate of clearance of specific drugs relative to an individual's genotypes is an important component in the interpretation of pharmacogenomic data for personalized medicine." [162]

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Metabolic ratios of psychotropics as indication of cytochrome P450 2D6/2C19 genotype
http://www.ncbi.nlm.nih.gov/pubmed/16044105 [171]

"The relationships between the observed metabolic ratios and CYP2D6 and/or CYP2C19 genotype were characterized using nonparametric statistical analysis. A clear correlation was observed between the CYP2D6 genotype and the metabolic ratio of venlafaxine." [171]

CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure
http://www.ncbi.nlm.nih.gov/pubmed/17301689 [186]

"Our study shows that (i) CYP2D6 diversity is far greater within than between populations and groups thereof, (ii) null or low-activity variants occur at high frequencies in various areas of the world, (iii) linkage disequilibrium is lowest in Africa and highest in the Americas. Patterns of variation, within and among populations, are similar to those observed for other autosomal markers (e.g. microsatellites and protein polymorphisms), suggesting that the diversity observed at the CYP2D6 locus reflects the same factors affecting variation at random genome markers." [186]

CYP2D6 genotype information to guide pimozide treatment in adult and pediatric patients: basis for the U.S. Food and Drug Administration's new dosing recommendations
http://www.ncbi.nlm.nih.gov/pubmed/23059146 [187]

"The occurrence of pimozide-induced arrhythmias is concentration dependent. Hence, it is important for prescribers to consider causes of increased pimozide exposure. This article summarizes the U.S. Food and Drug Administration's (FDA's) review of drug interaction and pharmacogenomic studies and discusses pharmacokinetic simulations we performed to develop new cytochrome P450 2D6 (CYP2D6) genotype-guided dosing recommendations for pimozide." [187]

Cytochrome P450 2D6 Phenotype Predicts Antidepressant Efficacy of Venlafaxine: A Secondary Analysis of 4 Studies in Major Depressive Disorder
http://www.ncbi.nlm.nih.gov/pubmed/20441720 [188]

"Compared with PMs, EMs had significantly greater mean changes from baseline on 4 of 5 depression rating scales (all 4 comparisons, $P \leq .020$). A significantly greater percentage of EMs achieved response or remission by most measures compared with PMs (4 of 5 comparisons, $P \leq .015$). Rates of discontinuation and AEs did not differ significantly between EMs and PMs." [188]

Clinical Pharmacokinetics of Atomoxetine
http://www.ncbi.nlm.nih.gov/pubmed/15910008 [189]

Effects of the CYP2D6*10 allele on the pharmacokinetics of atomoxetine and its metabolites
http://www.ncbi.nlm.nih.gov/pubmed/26254792 [190]

CYP2D6 predicted metabolizer status and safety in adult patients with attention-deficit hyperactivity disorder participating in a large placebo-controlled atomoxetine maintenance of response clinical trial
http://www.ncbi.nlm.nih.gov/pubmed/25919121 [191]

Several studies have shown that CYP2D6 polymorphims can lead to alterd Atomoxetine metabolism and varied blood levels, as well as increased risk of side effects. "The mean exposure to active moieties of atomoxetine was markedly higher in subjects with the CYP2D6*10/*10 genotype compared to that in those with the CYP2D6*wt/*wt genotype.[190]" "Poor metabolizers had higher frequencies of dry mouth, erectile dysfunction, hyperhidrosis, insomnia, and urinary retention compared with the other metabolizer groups. [191]" [189-191]

Cytochrome P450 2D6 genotype affects the pharmacokinetics of controlled-release paroxetine in healthy Chinese subjects: comparison of traditional phenotype and activity score systems
http://www.ncbi.nlm.nih.gov/pubmed/25967538 [192]

"The pharmacokinetics of controlled-release paroxetine after a single administration was affected by CYP2D6 polymorphisms. Both the traditional phenotype and the activity score systems performed well and distinguished subjects with different drug exposures. The activity score system provided a more detailed classification for the subjects." [192]

Genetics-Based Population Pharmacokinetics and Pharmacodynamics of Risperidone in a Psychiatric Cohort
http://www.ncbi.nlm.nih.gov/pubmed/26129906 [193]

"High interindividual variability in plasma concentrations of risperidone and its active metabolite, 9-hydroxyrisperidone, may lead to suboptimal drug concentration… Genetic polymorphisms of CYP2D6 play an important role in risperidone, 9-hydroxyrisperidone and active moiety plasma concentration variability, which were associated with common side effects. These results highlight the importance of a personalized dosage adjustment during risperidone treatment." [193]

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Impact of Multiple Inhibitors or Substrates of Cytochrome P450 2D6 on Plasma Risperidone Levels in Patients on Polypharmacy

http://www.ncbi.nlm.nih.gov/pubmed/18728628 [194]

"CYP2D6 catalyzes the conversion of risperidone to the active metabolite 9-OH-risperidone… Concentration-to-dose (C:D) ratios of risperidone and 9-OH-risperidone in 218 patients were associated with the number of concomitantly used substrates or inhibitors of CYP2D6. The C:D ratios of risperidone in patients with 0, 1, and >1 numbers of CYP2D6 inhibitors were 2.6, 8.5, and 17 nmol L^{-1} mg^{-1}, respectively. Differences between the groups were highly significant ($p < 0.001$). All patients with >1 CYP2D6 inhibitors were administered at least 1 potent CYP2D6 inhibitor, that is fluoxetine, paroxetine, thioridazine, and/or levomepromazine. The C:D ratios of the active moiety (risperidone + 9-OH-risperidone) in patients with 0, 1, and >1 numbers of concomitant CYP2D6 inhibitors were 17, 24, and 30 nmol L^{-1} mg^{-1}, respectively ($p = 0.001$), which was explained by higher levels of risperidone without any change in the levels of 9-OH-risperidone…An indication for risperidone drug monitoring should therefore include concomitant medication with established CYP inhibitors." [194]

CYP2D6 genetic polymorphisms and their relevance for poisoning due to amfetamines, opioid analgesics and antidepressants

http://www.ncbi.nlm.nih.gov/pubmed/25998998 [195]

"This review will focus specifically on CYP2D6 genetic polymorphisms and their relevance for poisoning due to amfetamines, opioid analgesics and antidepressants in humans…Either poor or extensive/ultra-rapid CYP2D6 metabolisers may be exposed to toxic effects of amfetamines, opioid analgesics and antidepressants. In these three categories, the level of evidence is substance dependent, with differences within the same pharmacological class." [195]

Opioid metabolism

http://www.ncbi.nlm.nih.gov/pubmed/19567715 [196]

"Clinicians understand that individual patients differ in their response to specific opioid analgesics and that patients may require trials of several opioids before finding an agent that provides effective analgesia with acceptable tolerability…This review describes the basics of opioid metabolism as well as the factors influencing it and provides recommendations for addressing metabolic issues that may compromise effective pain management." [196]

CYP2D6 phenotype-specific codeine population pharmacokinetics

http://www.ncbi.nlm.nih.gov/pubmed/25562725 [197]

"We aimed to develop a codeine pharmacokinetic pathway model for codeine and its metabolites that incorporates the effects of genetic polymorphisms… The population model indicated that about 10% of a codeine dose was converted to morphine in poor-metabolizer phenotype subjects. The model also showed that about 40% of a codeine dose was converted to morphine in EM subjects, and about 51% was converted to morphine in ultrarapid-metabolizers… Our study suggests that pharmacogenetics for personalized dosing might be most effectively advanced by studying the interplay between pharmacogenetics, population pharmacokinetics, and clinical pharmacokinetics." [197]

Individualized Hydrocodone Therapy Based on Phenotype, Pharmacogenetics, and Pharmacokinetic Dosing

http://www.ncbi.nlm.nih.gov/pubmed/?25621429 [198]

"Our results demonstrate that pharmacogenetics afford clinicians an opportunity to individualize [hydrocodone] HC dosing, while adding enhanced opportunity to account for its conversion to HM in the body." [198]

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1.19 Gene Tested: Cytochrome P450 3A4/5: (CYP3A4/5)

Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy
http://www.ncbi.nlm.nih.gov/pubmed/24151799 [7]

Pharmacogenetics of second-generation antipsychotics
http://www.ncbi.nlm.nih.gov/pubmed/24897292 [54]

The Human Cytochrome P450 (CYP) Allele Nomenclature Database
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PharmGKB The Pharmacogenomics Knowledgebase
https://www.pharmgkb.org/ [130]

Clinical applications of CYP genotyping in psychiatry
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [131]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [132]

Applications of CYP450 testing in the clinical setting
http://www.ncbi.nlm.nih.gov/pubmed/23588782 [150]

There is a large amount of variability in psychotropic drug response and variations in CYP450 genes, including CYP3A4/5, may impact this variability. There are several articles which review the relevant clinical implications of altered CYP3A4/5 metabolism. [7,54,129-132,150]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [133]

"Human liver samples and applied a systems biology approach via the integration of genetics, gene expression, and enzyme activity measurements. We found that most P450s were positively correlated among themselves and were highly correlated with known regulators as well as thousands of other genes enriched for pathways relevant to the metabolism of drugs, fatty acids, amino acids, and steroids. Genome-wide association analyses between genetic polymorphisms and P450 expression or enzyme activities revealed sets of SNPs associated with P450 traits, and suggested the existence of both cis-regulation of P450 expression (especially for CYP2D6) and more complex trans-regulation of P450 activity." [133]

CYP450 pharmacogenetic treatment strategies for antipsychotics: a review of the evidence
http://www.ncbi.nlm.nih.gov/pubmed/23870808 [134]

"CYP2D6, CYP1A2, and CYP3A4/5 are major enzymes in the metabolism of antipsychotics and polymorphisms of alleles for these proteins are associated with altered plasma levels… Numerous studies have shown a significant association between genotype and adverse effects, such as CYP2D6 polymorphisms and tardive dyskinesia. This review summarizes evidence for the role of CYP450 genetic variants in the response to antipsychotic medications and the clinical implications of pharmacogenetics in the management of patients with schizophrenia." [134]

The Dosing of Atypical Antipsychotics
http://www.ncbi.nlm.nih.gov/pubmed/15883149 [137]

"Dosage alterations of …quetiapine, dependent on cytochrome P450 3A (CYP3A), may be necessary when used with other drugs that inhibit or induce their metabolic enzymes. Genetic variations of cytochrome P450 2D6 (CYP2D6) and drug-drug interactions causing inhibition (CYP2D6 and/or CYP3A) or induction (CYP3A) may be important for risperidone, and perhaps for aripiprazole, dosing. Adding inhibitors may cause side effects more easily in drugs with a narrow therapeutic window, such as clozapine or risperidone, than in those with a wide therapeutic window, such as olanzapine or aripiprazole. Adding inducers may be associated with a gradual development of lost efficacy." [137]

CYP3A5 Genetic Polymorphisms in Different Ethnic Populations
http://www.ncbi.nlm.nih.gov/pubmed/15833928 [199]

"Cyp3A5 activity varies within any given ethnic population, suggesting that genetic variation within the Cyp3A5 gene may be the most important contributor to interindividual and interracial differences in Cyp3A-dependent drug clearance and response. …Significant differences were observed in the distribution of Cyp3A5*3, Cyp3A5*6, and Cyp3A5*7 alleles among white and African populations. The frequency of Cyp3A5*3 allele in white Canadians (93%) is higher than in Zimbabweans (77.6%) ($p < 0.001$). In contrast, Cyp3A5*6 and Cyp3A5*7 alleles are relatively frequent in African subjects (10–22%) but absent in white subjects ($p < 0.001$). These differences may reflect evolutionary pressures generated by environmental factors in geographically distinct regions. However, the genetic polymorphism of Cyp3A5 alone does not explain the interindividual differences in Cyp3A mediated metabolism." [199]

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Lurasidone drug-drug interaction studies: a comprehensive review

http://www.ncbi.nlm.nih.gov/pubmed/24825095 [200]

"Lurasidone PK is altered by strong cytochrome P450 (CYP) 3A4 inhibitors or inducers, and coadministration is contraindicated; whereas moderate CYP3A4 inhibitors have less effect, and lurasidone dosage restrictions are recommended." [200]

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