GENECEPT ASSAY

Literature Summary – Genecept Assay 2.0

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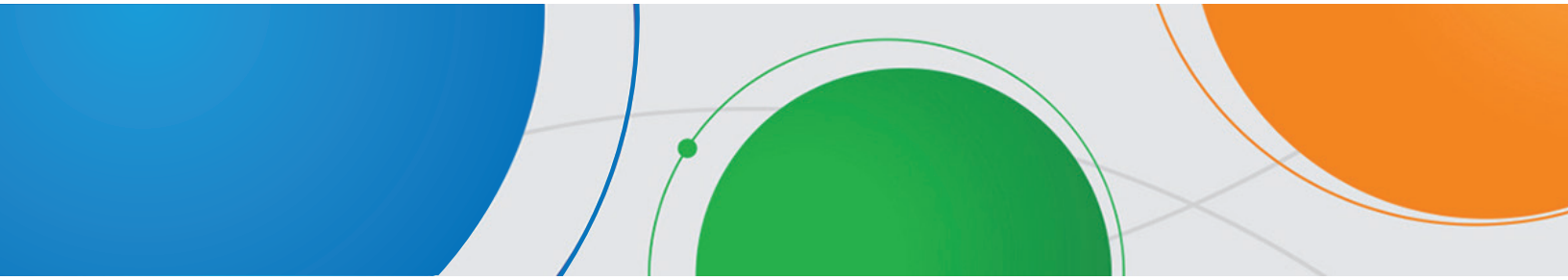

The following is a summary of the key published literature relevant to a variety of genetic variations. The purpose of this document is to summarize the information available. Individual patients vary and this information is not intended to replace the clinician's responsibilities in clinical decision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

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. 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]

Serotonin and Dopamine Gene Variation and Theory of Mind Decoding Accuracy in Major Depression: A Preliminary Investigation.

http://www.ncbi.nlm.nih.gov/pubmed/26974654 [13]

"Theory of mind-the ability to decode and reason about others' mental states-is a universal human skill and forms the basis of social cognition...Genetic associations were only found for the depressed group. Specifically, superior accuracy in decoding mental states of a positive valence was seen in those homozygous for the long allele of the serotonin transporter gene, 9-allele carriers of DAT1, and long-allele carriers of DRD4. In contrast, superior accuracy in decoding mental states of a negative valence was seen in short-allele carriers of the serotonin transporter gene and 10/10 homozygotes of DAT1. Results are discussed in terms of their implications for integrating social cognitive and neurobiological models of etiology in major depression." [13]

Interaction between SLC6A4 promoter variants and childhood trauma on the age at onset of bipolar disorders.

http://www.ncbi.nlm.nih.gov/pubmed/26542422 [14]

"Age at onset (AAO) of bipolar disorders (BD) could be influenced both by a repeat length polymorphism (5HTTLPR) in the promoter region of the serotonin transporter gene (SLC6A4) and exposure to childhood trauma. We assessed 308 euthymic patients with BD for the AAO of their first mood episode and childhood trauma. Patients were genotyped for the 5HTTLPR (long/short variant) and the rs25531. Genotypes were classified on functional significance (LL, LS, and SS)…These results remained significant after correction using FDR. Regression models suggested an interaction between emotional neglect and 'SS' genotype on the AAO (p = 0.009) and no further interaction with other trauma subtypes. Partial replication was obtained in the Brazilian sample, showing an interaction between emotional abuse and 'LS' genotype on the AAO (p = 0.02). In conclusion, an effect of childhood trauma on AAO of BD was observed only in patients who carry a specific stress responsiveness-related SLC6A4 promoter genotype." [14]

Maintenance of Chronic Fatigue Syndrome (CFS) in Young CFS Patients Is Associated with the 5-HTTLPR and SNP rs25531 A > G Genotype.

http://www.ncbi.nlm.nih.gov/pubmed/26473596 [15]

"Earlier studies have shown that genetic variability in the SLC6A4 gene encoding the serotonin transporter (5-HTT) may be important for the re-uptake of serotonin (5-HT) in the central nervous system. In the present study we investigated how the 5-HTT genotype i.e. the short (S) versus long (L) 5-HTTLPR allele and the SNP rs25531 A > G affect the physical and psychosocial functioning in patients with chronic fatigue syndrome (CFS). All 120 patients were recruited from The Department of Paediatrics at Oslo University Hospital, Norway, a national referral center for young CFS patients (12-18 years). Main outcomes were number of steps per day obtained by an accelerometer and disability scored by the Functional Disability Inventory (FDI). Patients with the 5-HTT SS or SLG genotype had a significantly lower number of steps per day than patients with the 5-HTT LALG, SLA or LALA genotype. Patients with the 5-HTT SS or SLG genotype also had a significantly higher FDI score than patients with the 5-HTT LALG, SLA or LALA genotype. Thus, CFS patients with the 5-HTT SS or SLG genotype had worse 30 weeks outcome than CFS patients with the 5-HTT LALG, SLA or LALA genotype. The present study suggests that the 5-HTT genotype may be a factor that contributes to maintenance of CFS." [15]

Role of the 5-HTTLPR and SNP Promoter Polymorphisms on Serotonin Transporter Gene Expression: a Closer Look at Genetic Architecture and In Vitro Functional Studies of Common and Uncommon Allelic Variants.

http://www.ncbi.nlm.nih.gov/pubmed/26464328 [16]

"The serotonin (5-hydroxytriptamine (5-HT)) transporter (5-HTT) gene-linked polymorphic region (5-HTTLPR) is a variable number tandem repeats (VNTR) located in the promoter region of the human 5-HTT-encoding gene SLC6A4. This length polymorphism gives rise to different promoter variants, variously influencing SLC6A4 expression. Over the years, an extensive literature has investigated the relationships between these promoter variants and SLC6A4 gene expression, since these variants have been variously associated to complex neuropsychiatric conditions and traits. In this review, we detail the genetic architecture of the 5-HTTLPR allelic variants reported so far, with a closer look at the two single nucleotide polymorphisms (SNPs) rs25531 and rs25532 that lies in the VNTR and thus increase genetic variability of the SLC6A4 promoter. We summarize the hypothesized molecular mechanisms underlying this variation. We also provide an update on common and uncommon 5-HTTLPR allelic variants reviewing the available data on functional in vitro analysis of their regulatory effect on SLC6A4 gene transcription. Controversial findings are highlighted and critically discussed. A deeper knowledge of the "5-HTTLPR universe" will be useful to better understand the molecular basis of serotonin homeostasis and the pathological basis underlying serotonin-related neuropsychiatric conditions and traits." [16]

Serotonin transporter polymorphism, memory and hippocampal volume in the elderly: association and interaction with cortisol.

https://www.ncbi.nlm.nih.gov/pubmed/17353910 [17]

"The s allele variant of the serotonin transporter gene (5-HTT) has recently been observed to moderate the relationship of stress to depression and anxiety… No impact or interactions of cumulative life stress with 5-HTT or cortisol were observed. This is the first investigation to identify an association of the 5-HTT s allele with poorer memory function in older adults. The interactive effects of the s allele and waking cortisol levels on reduced hippocampal volume and lower memory suggest that the negative effect of the serotonin polymorphism on memory is mediated by the HPA axis. Further, given the significant association of the s allele with higher waking cortisol in our investigation, future studies may be needed to evaluate the impact of the serotonin transporter polymorphism on any neuropsychiatric or behavioral outcome which is influenced by HPA axis function in older adults." [17]

HPA axis reactivity: a mechanism underlying the associations among 5-HTTLPR, stress, and depression.

https://www.ncbi.nlm.nih.gov/pubmed/18005940 [18]

"Recent evidence indicates that individuals who are homozygous for the short (s) allele in the promoter region of the serotonin transporter gene have higher rates of depression and other psychiatric disorders as a function of exposure to increasing levels of stressful life events than do individuals who have one or two copies of the long (l) allele. Despite the reliability of this association, the mechanism by which this polymorphism confers risk for psychopathology in the presence of stress is not understood. This study was designed to examine the formulation that individuals who are homozygous for the s allele are characterized by a greater biological reactivity to stress than are their counterparts who have one or two copies of the l allele. Girls at high (n = 25) and low (n = 42) risk for depression by virtue of the presence or absence of a family history of this disorder were genotyped and exposed to a standardized laboratory stress task. Cortisol levels were assessed before the stressor, after the stressor, and during an extended recovery period. Girls who were homozygous for the s allele produced higher and more prolonged levels of cortisol in response to the stressor than did girls with an l

allele. These findings indicate that the 5-HTTLPR polymorphism is associated with biological stress reactivity, which may increase susceptibility to depression in the face of stressful life events." [18]

The serotonin transporter promoter polymorphism is associated with cortisol response to psychosocial stress.
https://www.ncbi.nlm.nih.gov/pubmed/20006325 [19]

"Across multiple mental health-related measures, a polymorphism (5-HTTLPR) within the promoter of the serotonin transporter gene has been associated with differential psychological sensitivity to stressful experiences. Yet, the specific mechanisms by which this polymorphism contributes to risk for psychological dysfunction is unclear…Internal analyses revealed that the 5-HTTLPR was significantly associated with cortisol reactivity in the negative audience condition only, suggesting that short/short individuals might be especially vulnerable to social threat. The short/short genotype of the 5-HTTLPR is associated with greater cortisol reactivity to social threat. When short/short individuals experience stressful life events, they might be at greater risk for the adverse psychological and physical health consequences associated with heightened cortisol exposure." [19]

Genetic variants in serotonin and corticosteroid systems modulate neuroendocrine and cardiovascular responses to intense stress.
https://www.ncbi.nlm.nih.gov/pubmed/24821403 [20]

"Common variants in serotonin and corticosteroid receptor genes influence human stress in laboratory settings. Little is known of their combined effects, especially in high stress environments. This study evaluated distinct and combined effects of polymorphisms in the serotonin transporter (5HTTLPRL/S), glucocorticoid receptor (Bcl1C/G), and mineralocorticoid (-2C/G) receptor genes on adrenocortical and cardiovascular responses to intense, realistic stress. 5HTTLPR SS carriers revealed higher overall cortisol concentrations than L carriers. 5HTTLPR L carriers demonstrated higher stress-induced HR than non-carriers (SS) yet rebounded to a lower recovery value, while Bcl1 G carriers showed higher mean stress-induced HR than non-carriers (CC). This study revealed a synergistic effect of common polymorphisms on the acute stress response in healthy men. Pending additional study, these findings may have implications for drug discovery, gene therapy, and stress inoculation strategies." [20]

Genetic and environmental modulation of neurotrophic and anabolic stress response: Counterbalancing forces.
https://www.ncbi.nlm.nih.gov/pubmed/26136163 [21]

"The serotonin transporter genetic variant 5HTTLPR influences activation and feedback control of the hypothalamic-pituitary-adrenal axis, and has been shown to influence the effect of stressful life events on behavioral health… Distinct and interactive effects of 5HTTLPR long allele carriage [L] versus homozygous short allele carriage [SS]) and prior trauma exposure (low versus high) were evaluated, after which a priori group comparisons were performed between hypothesized high resilience (L/low) and low resilience (SS/high) groups. For sNGF, L/low produced the greatest sNGF throughout stress exposure while SS/high demonstrated the smallest; L/high and SS/low bisected these two extremes and were nearly identical to each other (i.e., SS/high < SS/low = L/high < L/low). Thus, 5HTTLPR and prior trauma exposure demonstrated counterbalancing (additive) forces. Similar patterns were found for DHEAS. To our knowledge, this study is the first to report counterbalancing genetic and environmental effects on novel biomarkers related to resilience in humans exposed to real-world stress. These findings have profound implications for health, performance and training in high-stress occupational settings." [21]

DNA methylation profiles within the serotonin transporter gene moderate the association of 5-HTTLPR and cortisol stress reactivity.
https://www.ncbi.nlm.nih.gov/pubmed/25226552 [22]

"The serotonin transporter gene-linked polymorphic region (5-HTTLPR) has been implicated in moderating vulnerability to stress-related psychopathology upon exposure to environmental adversity. A recent meta-analysis suggests a potential biological pathway conveying genotype-dependent stress sensitivity by demonstrating a small, but significant association of 5-HTTLPR and cortisol stress reactivity…Our results suggest that SLC6A4 methylation levels significantly moderate the association of 5-HTTLPR and cortisol stress reactivity. For individuals displaying low levels of SLC6A4 methylation, the S allele relates to increased cortisol stress reactivity in a dose-dependent fashion accounting for 7-9% of the variance in the endocrine stress response. By contrast, no such effect occurred under conditions of high SLC6A4 methylation, indicating that epigenetic changes may compensate for genotype-dependent differences in stress sensitivity. Studying epigenetic markers may advance gene-environment interaction research on 5-HTTLPR as they possibly capture the net effects of environmental influences relevant for stress-related phenotypes under serotonergic control." [22]

Progress and prospects in pharmacogenetics of antidepressant drugs.
https://www.ncbi.nlm.nih.gov/pubmed/27310483 [23]

"Depression is responsible for the most part of the personal and socio-economic burden due to psychiatric disorders. Since antidepressant response clusters in families, pharmacogenetics represents a meaningful tool to provide tailored treatments and improve the prognosis of depression. This review aims to summarize and discuss the pharmacogenetics of antidepressant drugs in major depressive disorder, with a focus on the most replicated genes, genome-wide association studies (GWAS), but also on the findings provided by new and promising analysis methods. In particular, multimarker tests such as pathway analysis and polygenic risk scores increase the power of detecting associations compared to the analysis of individual polymorphisms. Since genetic variants are not necessarily associated with a change in protein level, gene expression studies may provide complementary information to genetic studies. Finally, the pharmacogenetic tests that have been investigated for clinical application are discussed. Despite the lack of widespread clinical applications, preliminary results suggest that pharmacogenetics may be useful to guide antidepressant treatment. The US Food and Drug Administration included pharmacogenetic indications in the labeling of several antidepressants. This represented an important official recognition of the clinical relevance of genetic polymorphisms in antidepressant treatment." [23]

Pharmacogenetic studies: a tool to improve antidepressant therapy.
https://www.ncbi.nlm.nih.gov/pubmed/27889704 [24]

"The World Health Organization (WHO) predicts that major depressive disorder (MDD) will be the second leading cause of death and disability by 2020. Nowadays, approximately 60-70% of patients with this disorder have shown the lack of effectiveness and tolerability of the therapy with antidepressants. The US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) are including pharmacogenetic information in the labeling of several antidepressants. The presence of this information represents the relevance of genetic polymorphisms in drug response. These pharmacogenetic studies have been based on the knowledge of genes involved in pharmacokinetic (CYP2D6, CYP2C19 and ABCB1) and pharmacodynamic (SLC6A4, HTR2A, BDNF, GNB3 and FKBP5) processes of antidepressant medications. The knowledge of the genotype of patients with MDD is an important tool for personalized therapy that can improve their clinical response to treatment. In this review, we highlight the most relevant genes involved in the metabolism of antidepressants (ADs) or the genes related to the presence of adverse reactions." [24]

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 [25]

"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." [25]

Molecular neurobiological clues to the pathogenesis of bipolar disorder.
http://www.ncbi.nlm.nih.gov/pubmed/26210959 [26]

"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." [26]

Identification of pathways for bipolar disorder: a meta-analysis.
http://www.ncbi.nlm.nih.gov/pubmed/24718920 [27]

"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." [27]

Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder.
http://www.ncbi.nlm.nih.gov/pubmed/18711365 [28]

CACNA1C (Ca(v)1.2) in the pathophysiology of psychiatric disease.
http://www.ncbi.nlm.nih.gov/pubmed/22705413 [29]

Evidence for single nucleotide polymorphisms and their association with bipolar disorder.
http://www.ncbi.nlm.nih.gov/pubmed/24143106 [30]

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 [31]

Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4.
http://www.ncbi.nlm.nih.gov/pubmed/21926972 [32]

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 [33]

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 [34]

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) [28]. The results suggest that ion channelopathies may be involved in the pathogenesis of bipolar disorder. [28-34]

Genetic analysis of SNPs in CACNA1C and ANK3 gene with schizophrenia: A comprehensive meta-analysis.
http://www.ncbi.nlm.nih.gov/pubmed/26227746 [35]

Evaluating the association between CACNA1C rs1006737 and schizophrenia risk: A meta-analysis.
http://www.ncbi.nlm.nih.gov/pubmed/25588813 [36]

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) [31]." 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). [32, 35-36]

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 [37]

"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." [37]

CACNA1C gene and schizophrenia: a case-control and pharmacogenetic study.
http://www.ncbi.nlm.nih.gov/pubmed/26049408 [38]

"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." [38]

The effects of the CACNA1C rs1006737 A/G on affective startle modulation in healthy males.
http://www.ncbi.nlm.nih.gov/pubmed/25841664 [39]

"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." [39]

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 [40]

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. [40]

Association of rs1006737 in CACNA1C with alterations in prefrontal activation and fronto-hippocampal connectivity.
http://www.ncbi.nlm.nih.gov/pubmed/23404764 [41]

"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." [41]

CACNA1C genotype explains interindividual differences in amygdala volume among patients with schizophrenia.
http://www.ncbi.nlm.nih.gov/pubmed/23880959 [42]

"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." [42]

L-type voltage-dependent Ca2+ channels mediate expression of presynaptic LTP in amygdala.
http://www.ncbi.nlm.nih.gov/pubmed/19648911 [43]

"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." [43]

Effects of the CACNA1C risk allele on neurocognition in patients with schizophrenia and healthy individuals.
http://www.ncbi.nlm.nih.gov/pubmed/22957138 [44]

"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." [44]

The CACNA1C risk allele selectively impacts on executive function in bipolar type I disorder.
http://www.ncbi.nlm.nih.gov/pubmed/23406546 [45]

"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." [45]

Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression.
http://www.ncbi.nlm.nih.gov/pubmed/21903025 [46]

Efficacy of omega-3 fatty acids in mood disorders - a systematic review and metaanalysis.
http://www.ncbi.nlm.nih.gov/pubmed/19752840 [47]

A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression
http://www.ncbi.nlm.nih.gov/pubmed/20452573 [48]

Omega-3 polyunsaturated fatty acids for major depressive disorder.
http://www.ncbi.nlm.nih.gov/pubmed/24083675 [49]

"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." [46-49]

Functional Characterization of Schizophrenia-Associated Variation in CACNA1C.
http://www.ncbi.nlm.nih.gov/pubmed/27276213 [50]

"Calcium channel subunits, including CACNA1C, have been associated with multiple psychiatric disorders. Specifically, genome wide association studies (GWAS) have repeatedly identified the single nucleotide polymorphism (SNP) rs1006737 in intron 3 of CACNA1C to be strongly associated with schizophrenia and bipolar disorder. Here, we show that rs1006737 marks a quantitative trait locus for CACNA1C transcript levels. We test 16 SNPs in high linkage disequilibrium with rs1007637 and find one, rs4765905, consistently showing allele-dependent regulatory function in reporter assays. We find allele-specific protein binding for 13 SNPs including rs4765905. Using protein microarrays, we identify several proteins binding ≥3 SNPs, but not control sequences, suggesting possible functional interactions and combinatorial haplotype effects. Finally, using circular chromatin conformation capture, we show interaction of the disease-associated region including the 16 SNPs with the CACNA1C promoter and other potential regulatory regions. Our results elucidate the pathogenic relevance of one of the best-supported risk loci for schizophrenia and bipolar disorder." [50]

CACNA1C SNP rs1006737 associates with bipolar I disorder independent of the Bcl-2 SNP rs956572 variant and its associated effect on intracellular calcium homeostasis.
https://www.ncbi.nlm.nih.gov/pubmed/25843436 [51]

"SNP rs1006737 was significantly associated with BD-I. The [Ca (2+)] B was significantly higher in BD-I rs1006737 A compared with healthy A allele carriers and also in healthy GG compared with A allele carriers. There was no significant interaction between SNP rs1006737 and SNP rs956572 on [Ca (2+)] B." [51]

The Impact of the CACNA1C gene polymorphism on front limbic function in bipolar disorder.
https://www.ncbi.nlm.nih.gov/pubmed/21519340 [52]

CACNA1C risk variant and amygdala activity in bipolar disorder, schizophrenia and healthy controls.
https://www.ncbi.nlm.nih.gov/pubmed/23437284 [53]

"Several genetic studies have implicated the CACNA1C SNP rs1006737 in bipolar disorder (BD) and schizophrenia (SZ) pathology. This polymorphism was recently found associated with increased amygdala activity in healthy controls and patients with BD. We performed a functional Magnetic Resonance Imaging (fMRI) study in a sample of BD and SZ cases and healthy controls to test for altered amygdala activity in carriers of the rs1006737 risk allele (AA/AG), and to investigate if there were differences across the diagnostic groups… These results indicate that CACNA1C SNP rs1006737 affects amygdala activity during emotional processing across all diagnostic groups. The current findings add to the growing body of knowledge of the pleiotropic effect of this polymorphism, and further support that ion channel dysregulation is involved in the underlying mechanisms of BD and SZ." [53]

Phenotypic effects of a bipolar liability gene among individuals with major depressive disorder.
https://www.ncbi.nlm.nih.gov/pubmed/19388002 [54]

"Variations in voltage-dependent calcium channel L-type, alpha 1C subunit (CACNA1C) gene have been associated with bipolar disorder in a recent meta-analysis of genome-wide association studies. The impact of these variations on other psychiatric disorders has not been yet investigated. Caucasian non-Hispanic participants in the STAR*D study of treatment for depression for whom DNA was available (N = 1213) were genotyped at two single-nucleotide polymorphisms (SNPs) (rs10848635 and rs1006737) in the CACNA1C gene. We examined putative phenotypic indicators of bipolarity among patients with major depression and elements of longitudinal course suggestive of latent bipolarity. We also considered remission and depression severity following citalopram treatment. The rs10848635 risk allele was significantly associated with lower levels of baseline agitation (P = 0.03; beta = -0.09). The rs1006737 risk allele was significantly associated with lesser baseline depression severity (P = 0.04; beta = -0.4) and decreased likelihood of insomnia (P = 0.047; beta = -0.22). Both markers were associated with an increased risk of citalopram-emergent suicidality

(rs10848635: OR = 1.29, P = 0.04; rs1006737: OR = 1.34, P = 0.02). In this exploratory analysis, treatment-emergent suicidality was associated with two risk alleles in a putative bipolar liability gene." [54]

Common variants in CACNA1C and MDD susceptibility: A comprehensive meta-analysis.
https://www.ncbi.nlm.nih.gov/pubmed/27260792 [55]

"Major depressive disorder (MDD) is one of the most common psychiatric disorders with a relatively high heritability (35-40%). Though rs1006737 in the CACNA1C gene showed significant association with MDD in a British large-scale candidate association study, most of the replication analyses with relatively small sample size reported negative association… Rs1006737 showed significant association with MDD in the fixed-effect model (Z = 2.56, P = 0.011, OR = 1.08, 95%CI = 1.04-1.12) and the association remained after reanalyzing the data according to ethnicity. We additionally analyzed other 25 SNPs, genotyped in only one replication study, across the CACNA1C locus, and found that two SNPs, rs4765905 (P = 0.041, OR = 1.05, 95%CI 1.00-1.09) and rs4765937 (P = 0.025, OR = 1.05, 95%CI 1.01-1.09) showed nominal association with MDD, while rs2239073 (P = 0.002, OR = 1.07, 95%CI 1.02-1.11) exhibited significant association with MDD, which survived from multiple corrections. Our study provides support for positive association between CACNA1C and MDD; however, the current data suggest the necessity of replication analyses in a larger-scale sample." [55]

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 [26]

"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." [26]

Ankyrin-G regulates inactivation gating of the neuronal sodium channel, Nav1.6.
http://www.ncbi.nlm.nih.gov/pubmed/16775201 [56]

"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." [56]

Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder.
http://www.ncbi.nlm.nih.gov/pubmed/18711365 [28]

Evidence for single nucleotide polymorphisms and their association with bipolar disorder.
http://www.ncbi.nlm.nih.gov/pubmed/24143106 [30]

Two variants in Ankyrin 3 (ANK3) are independent genetic risk factors for bipolar disorder.
http://www.ncbi.nlm.nih.gov/pubmed/19088739 [57]

ANK3 as a risk gene for schizophrenia: new data in Han Chinese and meta analysis.
http://www.ncbi.nlm.nih.gov/pubmed/23109352 [58]

Ankyrin 3: genetic association with bipolar disorder and relevance to disease pathophysiology.
http://www.ncbi.nlm.nih.gov/pubmed/23025490 [59]

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 ($p = 9.1 \times 10^{-9}$) [28, 30, 57-59]

Genetic analysis of SNPs in CACNA1C and ANK3 gene with schizophrenia: A comprehensive meta-analysis.
http://www.ncbi.nlm.nih.gov/pubmed/26227746 [35]

"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." [35]

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 [37]

"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." [37]

Genome-wide supported risk variant for bipolar disorder alters anatomical connectivity in the human brain.

http://www.ncbi.nlm.nih.gov/pubmed/22079454 [60]

"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." [60]

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 [61]

"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." [61]

Genetic modulation of working memory deficits by ankyrin 3 gene in schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/24361380 [62]

"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." [62]

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 [63]

"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." [63]

The ANK3 bipolar disorder gene regulates psychiatric-related behaviors that are modulated by lithium and stress.

http://www.ncbi.nlm.nih.gov/pubmed/23237312 [64]

"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." [64]

Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression.

http://www.ncbi.nlm.nih.gov/pubmed/21903025 [46]

Efficacy of omega-3 fatty acids in mood disorders - a systematic review and metaanalysis.

http://www.ncbi.nlm.nih.gov/pubmed/19752840 [47]

A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression.
http://www.ncbi.nlm.nih.gov/pubmed/20452573 [48]

Omega-3 polyunsaturated fatty acids for major depressive disorder.
http://www.ncbi.nlm.nih.gov/pubmed/24083675 [49]

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. [46-49]

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 [65]

"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." [65]

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 [66]

"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." [66]

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 [67]

Pharmacogenetic Aspects of Antipsychotic Drug-induced Weight Gain - A Critical Review.
http://www.ncbi.nlm.nih.gov/pubmed/23431082 [68]

Polymorphisms of the HTR2C gene and antipsychotic-induced weight gain: an update and meta-analysis.
http://www.ncbi.nlm.nih.gov/pubmed/21121776 [69]

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. [68-69]

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 [70]

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. [70]

The 5-HT2C receptor and antipsychotic induced weight gain – mechanisms and genetics.
http://www.ncbi.nlm.nih.gov/pubmed/16785265 [71]

"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." [71]

Pharmacogenetics of second-generation antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/24897292 [72]

"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." [72]

Atypical antipsychotic-induced metabolic side effects: insights from receptor-binding profiles.
http://www.ncbi.nlm.nih.gov/pubmed/17848919 [73]

"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." [73]

Antipsychotic induced weight gain: genetics, epigenetics, and biomarkers reviewed.
http://www.ncbi.nlm.nih.gov/pubmed/25138234 [74]

"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." [74]

Role of serotonin 5-HT2C and histamine H1 receptors in antipsychotic-induced diabetes: A pharmacoepidemiological-pharmacodynamic study in VigiBase.
https://www.ncbi.nlm.nih.gov/pubmed/26256010 [75]

"Pharmacodynamic mechanisms of diabetes induced by antipsychotic drugs remain unclear, while numerous receptors have been suspected to be involved in the genesis of this Adverse Drug Reaction (ADR). We investigated potential relationships between antipsychotics' receptor occupancy (serotonin 5-HT1A, 5-HT2A, 5-HT2C, histamine H1, muscarinic M3, adrenergic α1, α2 or dopaminergic D2 D3 occupancies) and reports of diabetes using VigiBase®, the World Health Organization (WHO) global Individual Case Safety Report (ICSR) database… Using an original pharmacoepidemiological-pharmacodynamic (PE-PD) approach, our study supports that antipsychotic drugs blocking simultaneously histamine H1 and serotonin 5-HT2C receptors are more frequently associated with diabetes reports in VigiBase(®) than other antipsychotics. These findings should encourage investigation of histamine H1 and serotonin 5-HT2C properties for predicting the risk of glycemic effects in candidate antipsychotics." [75]

1.5 Gene Tested: Melanocortin 4 Receptor (MC4R)

Antipsychotic induced weight gain: genetics, epigenetics, and biomarkers reviewed.
http://www.ncbi.nlm.nih.gov/pubmed/25138234 [74]

"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." [74]

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 [76]

"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." [76]

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 [77]

"Melanocortin-4-receptor (MC4R) haplo-insufficiency 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." [77]

MC4R rs489693: a clinical risk factor for second generation antipsychotic-related weight gain?

http://www.ncbi.nlm.nih.gov/pubmed/23920449 [78]

"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." [78]

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 [79]

"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." [79]

Antipsychotic drugs and obesity.

http://www.ncbi.nlm.nih.gov/pubmed/21185230 [80]

"Mechanisms underlying antipsychotic cardio metabolic 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 effects. However, sophisticated molecular studies and genome-wide association studies, ideally in antipsychotic-naïve/first episode samples, are needed to further advance the field." [80]

Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review.

http://www.ncbi.nlm.nih.gov/pubmed/15998156 [81]

"Increasing numbers of reports concerning diabetes, ketoacidosis, hyperglycemia 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." [81]

Pharmacogenetic Associations of Antipsychotic Drug-Related Weight Gain: A Systematic Review and Meta-analysis.

http://www.ncbi.nlm.nih.gov/pubmed/27217270 [82]

"Altogether, 72 articles reporting on 46 non-duplicated samples (n = 6700, mean follow-up = 25.1wk) with 38 SNPs from 20 genes/genomic regions were meta-analyzed (for each meta-analysis, studies = 2-20, n = 81-2082). Eleven SNPs from 8 genes were significantly associated with weight or BMI change, and 4 SNPs from 2 genes were significantly associated with categorical weight or BMI increase. Combined, 13 SNPs from 9 genes (Adrenoceptor Alpha-2A [ADRA2A], Adrenoceptor Beta 3 [ADRB3], Brain-Derived Neurotrophic Factor [BDNF], Dopamine Receptor D2 [DRD2], Guanine Nucleotide Binding Protein [GNB3], 5-Hydroxytryptamine (Serotonin) Receptor 2C [HTR2C], Insulin-induced gene 2 [INSIG2], Melanocortin-4 Receptor [MC4R], and Synaptosomal-associated protein, 25kDa [SNAP25]) were significantly associated with antipsychotic-related weight gain (P-values < .05-.001). SNPs in ADRA2A, DRD2, HTR2C, and MC4R had the largest effect sizes (Hedges' g's = 0.30-0.80, ORs = 1.47-1.96). Less prior antipsychotic exposure (pediatric or first episode patients) and short follow-up (1-2 months) were associated with larger effect sizes. Individual antipsychotics did not significantly moderate effect sizes." [82]

1.6 Gene Tested: Dopamine 2 Receptor (DRD2)

Pharmacogenetics and antipsychotic treatment response.

http://www.ncbi.nlm.nih.gov/pubmed/26076775 [83]

"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." [83]

DRD2 promoter region variation predicts antipsychotic-induced weight gain in first episode schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/20664489 [84]

"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." [84]

Dopamine D2 receptor genetic variation and clinical response to antipsychotic drug treatment: A meta-analysis.

http://www.ncbi.nlm.nih.gov/pubmed/20194480 [85]

"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." [85]

Association of variants in DRD2 and GRM3 with motor and cognitive function in first-episode psychosis.

http://www.ncbi.nlm.nih.gov/pubmed/24682224 [86]

"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." [86]

Association between polymorphisms of DRD2 and DRD4 and opioid dependence: evidence from the current studies.

https://www.ncbi.nlm.nih.gov/pubmed/21714067 [87]

"Several studies have assessed the association between genetic polymorphisms of DRD2 and DRD4 genes and opioid dependence risk, while the results were inconsistent. We performed a meta-analysis, including 6,846 opioid dependence cases and 4,187 controls from 22 individual studies, to evaluate the roles of four variants (DRD2 -141ins/del C, rs1799732; DRD2 311 Ser > Cys, rs1801028; DRD2-related Taq1 A, rs1800497 and DRD4 exon III VNTR) in opioid dependence for the first time… In conclusion, our results suggested that DRD2 -141ins/del C, DRD2-related TaqI A and DRD4 exon III VNTR polymorphisms might play important roles in the development of opioid dependence." [87]

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 [88]

"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." [88]

Neurogenetics and pharmacology of learning, motivation, and cognition.

http://www.ncbi.nlm.nih.gov/pubmed/20631684 [89]

"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." [89]

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 [90]

"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)." [90]

Inverted-U-shaped dopamine actions on human working memory and cognitive control.

http://www.ncbi.nlm.nih.gov/pubmed/21531388 [91]

"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." [91]

Role of dopamine in the motivational and cognitive control of behavior.

http://www.ncbi.nlm.nih.gov/pubmed/18660464 [92]

"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." [92]

COMT genotype and response to cognitive remediation in schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/26255563 [93]

"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." [93]

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 [94]

"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." [94]

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 [95]

"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 micro-dialysis. 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." [95]

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 [96]

"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 extra-striatal 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 extra-striatal 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." [96]

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 [97]

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

http://www.ncbi.nlm.nih.gov/pubmed/21849980 [98]

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 [99]

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

http://www.ncbi.nlm.nih.gov/pubmed/19890238 [100]

The expanding evidence base for rTMS treatment of depression.

http://www.ncbi.nlm.nih.gov/pubmed/23154644 [101]

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. 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." [97-101]

The COMT Val158Met polymorphism moderates the association between cognitive functions and white matter microstructure in schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/26999687 [102]

"Impaired cognitive functioning is a core feature of schizophrenia. Cognitive impairment in schizophrenia has been associated with white-matter (WM) abnormalities and degenerative changes of cortical myelin in the cerebral cortex. Furthermore, findings suggested a role of the COMT gene in affecting both WM and neuropsychological performances. We thus hypothesized that the COMT Val/ Met genotype would affect the association between cognitive functions and WM microstructure in a sample of schizophrenic patients….Analysis indicated an association between cognitive functions and WM microstructure in the Val/Val group, but not in the Met carriers group. WM tracts include the corpus callosum, thalamic radiations, corona radiata, forceps major and minor, superior and inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, corticospinal tract, and cingulum." [102]

Treatment of cognitive deficits associated with schizophrenia: potential role of catechol-O-methyltransferase inhibitors

http://www.ncbi.nlm.nih.gov/pubmed/17579498 [103]

"…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." [103]

Tolcapone improves cognition and cortical information processing in normal human subjects

http://www.ncbi.nlm.nih.gov/pubmed/17063156 [104]

"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." [104]

Diverse facets of COMT: from a plausible predictive marker to a potential drug target for schizophrenia.

https://www.ncbi.nlm.nih.gov/pubmed/21999147 [105]

Dopaminergic system in the prefrontal cortex (PFC) is known to regulate the cognitive functions. Catechol-O-methyl transferase (COMT), one of the major modulators of prefrontal dopamine function, has emerged as an important determinant of schizophrenia associated cognitive dysfunction and response to antipsychotics. A common Val->Met polymorphism (rs4680) in the COMT gene, associated with increased prefrontal dopamine catabolism, impairs prefrontal cognition and might increase risk for schizophrenia. Further, the degree of cognitive improvement observed with antipsychotics in schizophrenia patients is influenced by the COMT activity, and Val/Met has been proposed as a potential pharmacogenetic marker. However, studies evaluating the role of COMT have been equivocal. The presence of other functional polymorphisms in the gene, and the observed ethnic variations in the linkage disequilibrium structure at COMT locus, suggest that COMT activity regulation might be complex. Despite these lacunae in our current understanding, the influence of COMT on PFC mediated cognitive tasks is undeniable. COMT thus represents an attractive candidate for novel therapeutic interventions for cognitive dysfunction. The COMT activity inhibiting drugs including tolcapone and entacapone, have shown promising potential as they selectively modulate dopaminergic transmission. This review is an attempt to summarize the rapidly evolving literature exploring the diverse facets of COMT biology, its functional relevance as a predictive marker and a therapeutic target for schizophrenia." [105]

Genotype-Dependent Effects of COMT Inhibition on Cognitive Function in a Highly Specific, Novel Mouse Model of Altered COMT Activity..

https://www.ncbi.nlm.nih.gov/pubmed/27388330 [106]

"…We therefore developed a novel mouse model of altered COMT activity. The human Met allele was introduced into the native mouse COMT gene to produce COMT-Met mice, which were compared with their wild-type littermates. The model proved highly specific: COMT-Met mice had reductions in COMT abundance and activity, compared with wild-type mice, explicitly in the absence of off-target changes in the expression of other genes. Despite robust alterations in dopamine metabolism, we found only subtle changes on certain cognitive tasks under baseline conditions (e.g, increased spatial novelty preference in COMT-Met mice vs wild-type mice). However, genotype differences emerged after administration of the COMT inhibitor tolcapone: performance of wild-type mice, but not COMT-Met mice, was improved on the 5-choice serial reaction time task after tolcapone administration. There were no changes in anxiety-related behaviors in the tests that we used. Our findings are convergent with human studies of the Val158Met polymorphism, and suggest that COMT's

effects are most prominent when the dopamine system is challenged. Finally, they demonstrate the importance of considering COMT genotype when examining the therapeutic potential of COMT inhibitors." [106]

Improvement of prepulse inhibition and executive function by the COMT inhibitor tolcapone depends on COMT Val158Met polymorphism.

https://www.ncbi.nlm.nih.gov/pubmed/18536698 [107]

"Recent evidence suggests that pre-pulse inhibition (PPI) levels relate to executive function possibly by a prefrontal cortex (PFC) dopamine (DA) link. We explored the effects of enhanced PFC DA signaling by the nonstimulant catechol-O-methyltransferase (COMT) inhibitor tolcapone, on PPI and working memory of subjects homozygous for the Val (low PFC DA) and the Met (high PFC DA) alleles of the COMT Val158Met polymorphism…These results suggest that early information processing and working memory may both depend on PFC DA signaling, and that they may both relate to PFC DA levels according to an inverted U-shaped curve function." [107]

COMT Val (158) Met genotype determines the direction of cognitive effects produced by catechol-O-methyltransferase inhibition.

https://www.ncbi.nlm.nih.gov/pubmed/22364739 [108]

"Catechol-O-methyltransferase (COMT) metabolizes dopamine. The COMT Val (158) Met polymorphism influences its activity, and multiple neural correlates of this genotype on dopaminergic phenotypes, especially working memory, have been reported. COMT activity can also be regulated pharmacologically by COMT inhibitors. The inverted-U relationship between cortical dopamine signaling and working memory predicts that the effects of COMT inhibition will differ according to COMT genotype…Depending on genotype, COMT inhibition can enhance or impair working memory and increase or decrease risky decision making. To our knowledge, the data are the clearest demonstration to date that the direction of effect of a drug can be influenced by a polymorphism in its target gene. The results support the inverted-U model of dopamine function. The findings are of translational relevance, because COMT inhibitors are used in the adjunctive treatment of Parkinson's disease and are under evaluation in schizophrenia and other disorders." [108]

Effect of tolcapone on brain activity during a variable attentional control task: a double-blind, placebo-controlled, counter-balanced trial in healthy volunteers.

https://www.ncbi.nlm.nih.gov/pubmed/23794107 [109]

"Attention is the capacity to flexibly orient behaviors and thoughts towards a goal by selecting and integrating relevant contextual information. The dorsal cingulate (dCC) and prefrontal (PFC) cortices play critical roles in attention. Evidence indicates that catechol-O-methyltransferase (COMT) modulates dopaminergic tone in the PFC and dCC… Our results show that pharmacological reduction of COMT activity modulates the engagement of attentional mechanisms, selectively enhancing the efficiency of dCC processing in healthy volunteers, reflected as decreased activity for the same level of performance." [109]

Tolcapone, COMT polymorphisms and pharmacogenomic treatment of schizophrenia.

https://www.ncbi.nlm.nih.gov/pubmed/21521027 [110]

"It is widely accepted that abnormal prefrontal cortex biology resulting in deficient cognition is a primary problem in schizophrenia and that all currently available antipsychotics fail to improve cognitive and negative symptoms originating from this deficit. Evidence from basic science has revealed the importance of prefrontal dopamine signaling for optimal prefrontal function. This article describes succinctly the progress made so far, taking into account the mechanisms involved in catechol-O-methyltransferase (COMT)-induced modulation of prefrontal dopamine signaling, the impact of COMT on cognitive function and the role of COMT gene polymorphisms. The potential role of the COMT inhibitor tolcapone to improve cognitive function in health and disease is also presented here. It will soon be understood if tolcapone represents one of the first hypothesis-driven, biology-based, genotype-specific, targeted treatments of cognitive and negative symptoms of schizophrenia." [110]

1.8 Gene Tested: Catechol-O-Methyltransferase (COMT; Met/Met genotype)

Effect of COMT val158met genotype on cognition and personality.

http://www.ncbi.nlm.nih.gov/pubmed/18755576 [88]

"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

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http://www.ncbi.nlm.nih.gov/pubmed/20631684 [89]

"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." [89]

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 [90]

"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)." [90]

Inverted-U-shaped dopamine actions on human working memory and cognitive control.
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Role of dopamine in the motivational and cognitive control of behavior.
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"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, not least because they implicate paradoxical changes in distinct dopamine systems that innervate dissociable neural circuits. 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." [92]

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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." [93]

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 [94]

"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." [94]

Catechol-O-Methyltransferase Val158Met Polymorphism and Clinical Response to Antipsychotic Treatment in Schizophrenia and Schizo-Affective Disorder Patients: a Meta-Analysis.
http://www.ncbi.nlm.nih.gov/pubmed/26745992 [111]

"Ten studies met inclusion criteria for the meta-analysis. Five additional antipsychotic-treated samples were analyzed for Val158Met and response and included in the meta-analysis (total=1416). Met/Met individuals were significantly more likely to respond than Val-carriers (P=.039, OR Met/Met=1.37, 95% CI: 1.02-1.85). Met/Met patients also experienced significantly greater improvement in positive symptoms relative to Val-carriers (P=.030, SMD=0.24, 95% CI: 0.024-0.46). Posthoc analyses on patients treated with atypical antipsychotics (n=1207) showed that Met/Met patients were significantly more likely to respond relative to Val-carriers (P=.0098, OR Met/Met=1.54, 95% CI: 1.11-2.14), while no difference was observed for typical-antipsychotic-treated patients (n=155) (P=.65)." [111]

COMT val158met moderation of dopaminergic drug effects on cognitive function: a critical review.
http://www.ncbi.nlm.nih.gov/pubmed/27241058 [112]

"The relationship between dopamine (DA) tone in the prefrontal cortex (PFC) and PFC-dependent cognitive functions (for example, working memory, selective attention, executive function) may be described by an inverted-U-shaped function, in which both excessively high and low DA is associated with impairment. In the PFC, the COMT val158met single nucleotide polymorphism (rs4680) confers differences in catechol-O-methyltransferase (COMT) efficacy and DA tone, and individuals homozygous for the Val allele display significantly reduced cortical DA. Many studies have investigated whether val158met genotype moderates the effects of dopaminergic drugs on PFC-dependent cognitive functions. A review of 25 such studies suggests evidence for this pharmacogenetic effect is mixed for stimulants and COMT inhibitors, which have greater effects on D1 receptors, and strong for antipsychotics, which have greater effects on D2 receptors. Overall, COMT val158met genotype represents an enticing target for identifying individuals who are more likely to respond positively to dopaminergic drugs." [112]

COMT genetic variation and clinical response to antipsychotic drug treatment: A Meta-analysis.
https://www.ncbi.nlm.nih.gov/pubmed/26164511 [113]

"Nine studies included 868 participants met inclusion criteria. Significant association was found between the COMT Val108/158Met gene polymorphism and antipsychotic drug efficacy. Evaluating the therapeutic efficacy through general symptoms: Met vs Val, RR=1.18, 95% CI: 1.04-1.35, P=0.013; Met/Met vs Val/Val, RR=1.40, 95% CI: 1.08-1.82, P=0.010. Evaluating the therapeutic efficacy through negative symptoms: Met vs Val, RR=1.24, 95% CI: 1.05-1.46, P=0.013; Met/Met vs Val/Val, RR=1.60, 95% CI: 1.04-2.46, P=0.031.COMT Val108/158Met gene polymorphism is significantly associated with antipsychotic drug efficacy, and Met gene is a dominant gene which displays a better response to antipsychotic drugs." [113]

COMT (Val (158/108) Met) genotype moderates the impact of antipsychotic medication on verbal IQ in twins with schizophrenia.
https://www.ncbi.nlm.nih.gov/pubmed/21233783 [114]

"In this study, we aimed to assess the moderating effects of the catechol-O-methyl transferase (COMT) (Val (158/108) Met) genotype on antipsychotic medication-induced changes in the cognitive performance of patients with chronic schizophrenia. The sample consisted of 85 monozygotic and 53 dizygotic twin pairs, of varying concordance for schizophrenia, and healthy control twins. Cognitive ability was measured using the Wechsler Adult Intelligence Scale-third edition. We used structural equation modelling to estimate main and interaction effects of the COMT status and antipsychotic medication dose on verbal intelligence quotient (VIQ) and performance intelligence quotient scores…Our results show that the verbal abilities of Val homozygotes of the COMT gene are cognitively impaired by higher doses of antipsychotic medication. This association is reversed in Met carriers. These data are consistent with an earlier study that found evidence of moderating effects of antipsychotic medication on N-back and verbal fluency tasks." [114]

Antipsychotic medications and cognitive functioning in bipolar disorder: moderating effects of COMT Val108/158 Met genotype.
https://www.ncbi.nlm.nih.gov/pubmed/23421957 [115]

"There is a negative association between the use of antipsychotics and cognitive functioning in bipolar patients, which may be mediated by altered dopamine signaling in selected brain areas, and moderation thereof by genetic sequence variation such as COMT Val108/158Met. The interaction between antipsychotic drug use and the COMT Val108/158Met genotype on two-year cognitive functioning in bipolar patients was examined…The negative effects of antipsychotics on cognitive functioning in bipolar disorder may be moderated by the COMT Val 108/158 Met genotype, with a negative effect of Val allele load. If replicated, the results may be indicative of pharmacogenetic interactions in bipolar disorder." [115]

COMT val108/158met genotype, cognitive function, and cognitive improvement with clozapine in schizophrenia.
https://www.ncbi.nlm.nih.gov/pubmed/17123785 [116]

"Preliminary evidence suggests that a single nucleotide polymorphism (SNP), the val108/158met SNP, within the gene that codes for catechol-O-methyltransferase (COMT), a key enzyme involved in regulating dopamine (DA) transmission within the prefrontal cortex (PFC), is related to cognitive function in schizophrenia and cognitive improvement with atypical antipsychotic drugs (APDs)... Consistent with several previous studies, an association between COMT genotype and tests of executive function and working memory was identified at baseline. In addition, a novel interaction between genotype and improvement on tests of attention and verbal fluency was identified. Specifically, met homozygous and Val/ Met heterozygous patients demonstrated significantly greater improvement than Val homozygous patients following 6 months of treatment with clozapine. The results are discussed in relation to previous cross-sectional studies and prospective investigations of the associations between COMT genotype, cognition, and cognitive improvement with atypical APDs in schizophrenia." [116]

Catechol-O-methyltransferase val108/158met genotype predicts working memory response to antipsychotic medications.

https://www.ncbi.nlm.nih.gov/pubmed/15522252 [117]

"The gene encoding catechol-O-methyltransferase (COMT), an enzyme that regulates prefrontal cortex dopamine, contains a common functional polymorphism (Val (108/158) Met) that influences prefrontal cortex function in an allelic dose-dependent manner. A recent study reported that the COMT Val (108/158) Met polymorphism influences cognitive- and physiologic-related prefrontal cortex responses to antipsychotic treatment. The present study tested the effects of several COMT polymorphisms on the cognitive response to antipsychotic medication in patients with schizophrenia…These results support other data suggesting that the COMT Val (108/158) Met polymorphism might be an important factor in the cognitive response to antipsychotic medication." [117]

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

Alpha-2 adrenergic receptors and attention-deficit/hyperactivity disorder.

http://www.ncbi.nlm.nih.gov/pubmed/20652773 [118]

"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." [118]

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 [119]

"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." [119]

The use of α-2A adrenergic agonists for the treatment of attention-deficit/hyperactivity disorder.

http://www.ncbi.nlm.nih.gov/pubmed/20925474 [120]

"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." [120]

Clinical utility of guanfacine extended release in the treatment of ADHD in children and adolescents.

http://www.ncbi.nlm.nih.gov/pubmed/26170637 [121]

"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." [121]

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 [122]

"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." [122]

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 [123]

"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." [123]

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

http://www.ncbi.nlm.nih.gov/pubmed/18200436 [124]

"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." [124]

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 [125]

"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." [125]

1.10 Gene Tested: Methylenetetrahydrofolate Reductase (MTHFR)

L-Methylfolate: A Vitamin for Your Monoamines.

http://www.ncbi.nlm.nih.gov/pubmed/19193337 [126]

Vitamins, Monoamines, and Depression.

http://primarypsychiatry.com/vitamins-monoamines-and-depression/ [127]

"Synthesis of the three monoamine neurotransmitters, serotonin, dopamine, and norpepinephrine, is regulated by L-methylfolate." "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." [127]

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

http://www.ncbi.nlm.nih.gov/pubmed/23831680 [128]

"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)." [128]

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

http://www.ncbi.nlm.nih.gov/pubmed/17074966 [129]

"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." [129]

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 [130]

"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." [130]

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 [131]

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/ [132]

Several studies have demonstrated l-methylfolate as an effective augmentation strategy with SSRI/SNRIs. [131-132]

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 [133]

"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." [133]

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 [134]

"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." [134]

Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism: epidemiology, metabolism and the associated diseases.

http://www.ncbi.nlm.nih.gov/pubmed/25449138 [135]

"The Methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism is associated with various diseases (vascular, cancers, neurology, diabetes, psoriasis, etc.) with the epidemiology of the polymorphism of the C677T that varies dependent on the geography and ethnicity. The 5, 10-Methylenetetrahydrofolate reductase (MTHFR) locus is mapped on chromosome 1 at the end of the short arm (1p36.6). This enzyme is important for the folate metabolism which is an integral process for cell metabolism in the DNA, RNA and protein methylation. The mutation of the MTHFR gene which causes the C677T polymorphism is located at exon 4 which results in the conversion of valine to alanine at codon 222, a common polymorphism that reduces the activity of this enzyme. The homozygous mutated subjects have higher homocysteine levels while the heterozygous mutated subjects have mildly raised homocysteine levels compared with the normal, non-

mutated controls. Hyperhomocysteinemia is an emerging risk factor for various cardiovascular diseases and with the increasing significance of this polymorphism in view of the morbidity and mortality impact on the patients, further prevention strategies and nutritional recommendations with the supplementation of vitamin B12 and folic acid which reduces plasma homocysteine level would be necessary as part of future health education. This literature review therefore focuses on the recent evidence-based reports on the associations of the MTHFR C677T polymorphism and the various diseases globally." [135]

Correlation of clinical response with homocysteine reduction during therapy with reduced B vitamins in patients with MDD who are positive for MTHFR C677T or A1298C polymorphism: a randomized, double-blind, placebo-controlled study.

http://www.ncbi.nlm.nih.gov/pubmed/27035272 [136]

"159 of 170 vitamin-treated patients and 123 of 160 placebo-treated patients were completers. Of the active treatment group, 131 (82.4%) showed a reduction in homocysteine (for a mean in this subgroup of 25%, p < .001), while 28 (17.6%) showed no significant change. Placebo patients demonstrated a small elevation in homocysteine. Active-treatment patients demonstrated, on average, a 12-point reduction on the MADRS by week 8, and 42% achieved full remission (p < .001). No side effect was significantly different between groups. No patients experienced mania." [136]

Role of MTHFR C677T gene polymorphism in the susceptibility of schizophrenia: An updated meta-analysis.

http://www.ncbi.nlm.nih.gov/pubmed/27025471 [137]

"Total 38 studies with 10,069 cases and 13,372 controls were included in the present meta-analysis. Results of meta-analysis showed significant associated between C677T polymorphism and risk of schizophrenia (OR T vs C=1.18, 95%CI=1.10-1.27, p=<0.001; OR CT vs CC=1.10, 95%CI=1.04-1.17, p=<0.001; OR TT vs CC=1.40, 95%CI=1.20-1.64, p=<0.001; OR TT + CT vs CC=1.19, 95%CI=1.09-1.30, p=<0.001). We also performed subgroup and sensitivity analyses. Subgroup analysis was done according to ethnicity and significant association was found between C677T polymorphism and risk of schizophrenia in all three ethnic populations-African (OR=2.51; 95%CI=1.86-3.40; p=<0.001), Asian (OR=1.21; 95%CI=1.10-1.33; p=<0.001) and Caucasian (OR=1.07; 95%CI=1.01-1.14; p=0.01). In conclusion the results of the present meta-analysis suggested that the MTHFR C677T polymorphism is a risk factor for schizophrenia." [137]

The C677T variant in MTHFR modulates associations between blood-based and cerebrospinal fluid biomarkers of neurodegeneration.

https://www.ncbi.nlm.nih.gov/pubmed/27380243 [138]

"The C677T functional variant in the methylene-tetrahydrofolate reductase (MTHFR) gene results in reduced enzymatic activity and elevated blood levels of homocysteine. Plasma levels of apolipoprotein E (ApoE) are negatively correlated with cerebral amyloid burden, but plasma homocysteine concentrations are associated with increased amyloid-β (Aβ) deposition in the brain…This modulation by the MTHFR genotype did not remain significant after controlling for ApoE genotype. In T-homozygotes who do not carry the ApoE-ε4 allele, the relationship between low plasma ApoE levels and an increased risk of dementia is likely obscured by the presence of elevated plasma homocysteine. This report suggests the value of genotyping patients at the C677T functional variant when using plasma ApoE levels as a preclinical biomarker for Alzheimer's disease." [138]

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 [139]

"A single-nucleotide polymorphism 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." [139]

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

http://www.ncbi.nlm.nih.gov/pubmed/24910563 [140]

"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." [140]

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

http://www.ncbi.nlm.nih.gov/pubmed/18852698 [141]

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

http://www.ncbi.nlm.nih.gov/pubmed/24433458 [142]

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. [141-142]

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

http://www.ncbi.nlm.nih.gov/pubmed/22610920 [143]

"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." [143]

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 [144]

"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 hyper activations 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." [144]

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

http://www.ncbi.nlm.nih.gov/pubmed/18497103 [145]

"…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 behaviors 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." [145]

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 [146]

"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." [146]

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 [147]

"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." [147]

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

http://www.ncbi.nlm.nih.gov/pubmed/24760847 [148]

"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 Nucleus Accumbens. Conversely, BDNF Met (66) carriers showed no activation in response to monetary gains and a blunted DA response to the analgesic placebo in the nucleus accumbens. 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- Nucleus Accumbens pathway. Our results are of relevance to the neurobiology of stress and reward interactions and the pathophysiology of stress-related disorders." [148]

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

http://www.ncbi.nlm.nih.gov/pubmed/22442074 [149]

"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 hyper reactivity, 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." [149]

Effects of BDNF polymorphisms on antidepressant action.

http://www.ncbi.nlm.nih.gov/pubmed/21253406 [150]

"In human BDNF gene, there is a common functional polymorphism (Val66Met) in the pro-region of BDNF, which affects the intracellular trafficking of pro-BDNF. 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." [150]

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

http://www.ncbi.nlm.nih.gov/pubmed/20167454 [151]

"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." [151]

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

http://www.ncbi.nlm.nih.gov/pubmed/25658497 [152]

"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." [152]

BDNF and CREB1 genetic variants interact to affect antidepressant treatment outcomes in geriatric depression.
http://www.ncbi.nlm.nih.gov/pubmed/23619509 [153]

"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." [153]

BDNF Val66Met impairs fluoxetine-induced enhancement of adult hippocampus plasticity.
http://www.ncbi.nlm.nih.gov/pubmed/22218094 [154]

"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." [154]

A behavioral analysis of the impact of voluntary physical activity on hippocampus-dependent contextual conditioning.
http://www.ncbi.nlm.nih.gov/pubmed/19115374 [155]

"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 sub-regions 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." [155]

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 [156]

"…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." [156]

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 [157]

"...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." [157]

Identifying genetic predictors of depression risk: 5-HTTLPR and BDNF Val66Met polymorphisms are associated with rumination and co-rumination in adolescents.
https://www.ncbi.nlm.nih.gov/pubmed/24312122 [158]

"…In Study I, the Val66Met single-nucleotide polymorphism (SNP) was associated with rumination in adolescents, but not children, such that adolescents homozygous for the Val allele reported higher rumination levels. Further, a cumulative genetic score (CGS) (Val66Val and 5-HTTLPR) predicted higher levels of co-rumination, specifically among adolescent girls. Both genetic associations maintained significance after covariation for current depressive symptomology, and the other endophenotype. Finally, both genetic associations exhibited similar effect sizes in Study II, although results did not reach statistical significance…he current study indicates that candidate genes may demonstrate utility as consistent genetic markers of depression risk when focused on specific phenotypes, and supports the need to explore potential differential effects of developmental stage and sex." [158]

Pharmacogenetics in major depression: a comprehensive meta-analysis.
https://www.ncbi.nlm.nih.gov/pubmed/23733030 [159]

"A number of candidate gene studies focused on major depression (MD) and antidepressant (AD) efficacy have been carried out, but results mainly remain inconclusive. We performed a comprehensive meta-analysis of published candidate gene studies focused on AD efficacy in MD to evaluate the cumulative evidence. A random-effect model was applied to study the polymorphisms with genotypic counts available from at least three independent studies. On the base of previous evidence, the analysis was stratified by ethnicity (Caucasian, Asian, and other/mixed), and AD class (SSRIs and mixed/other ADs). Genotypic data were available for 16 polymorphisms in 11 genes. After the exclusion of 5-HTTLPR in SLC6A4 included in another recent meta-analysis, 15 polymorphisms in 11 genes were included in the present meta-analysis (BDNF rs6265, SLC6A4 STin2, HTR1A rs6295, HTR2A rs6311, rs6313 and rs7997012, HTR6 rs1805054, TPH1 rs1800532, SLC6A2 rs5569, COMT rs4680, GNB3 rs5443, FKBP5 rs1360780 and rs3800373, and ABCB1 rs1045642 and rs2032582). Our results suggested that BDNF rs6265 (Val66Met) heterozygous genotype was associated with better SSRIs response compared to the homozygous genotypes, particularly in Asians (OR=1.53, 95%CI 1.12-2.07, p=0.007). SLC6A4 STin2, HTR2A rs6311 and rs7997012, GNB3 rs5443, FKBP5 rs1360780 and rs3800373, and ABCB1 rs2032582 showed associations with AD efficacy, but these results were highly dependent on one or two single studies. In conclusion, our findings suggested the BDNF Val66Met as the best single candidate involved in AD response, with a selective effect on SSRI treatment. Our overall results supported no major effect of any single gene variant on AD efficacy." [159]

Association of BDNF Val66MET Polymorphism with Parkinson's Disease and Depression and Anxiety Symptoms.
https://www.ncbi.nlm.nih.gov/pubmed/27852165 [160]

"An association between Parkinson's disease (PD) and brain-derived neurotrophic factor (BDNF) was suggested by several studies, with contradictory results. BDNF is necessary for the survival of dopaminergic neurons in substantia nigra. Val66Met is a common polymorphism of the BDNF gene that affects cognitive and motor processes. The authors studied 104 Brazilian patients with PD and 96 control participants. The G/G genotype was significantly associated with depression and anxiety symptoms and development of PD. This is the first study that associates this genotype with PD." [160]

Altered Episodic Memory in Introverted Young Adults Carrying the BDNF Met Allele.
https://www.ncbi.nlm.nih.gov/pubmed/27845759 [161]

"While most studies have been interested in the distinct, predisposing roles of the common BDNF Val66Met variant and extraversion personality traits on episodic memory, very few studies have looked at the synergistic effects of genetic and personality factors to account for cognitive variance… Subsequent correlational analyses yielded a strong and significant correlation ($r = 0.542$; $p < 0.005$) between introversion and delayed episodic memory specific to BDNF Met individuals. The present study suggests that introversion and the BDNF Met variant synergistically interact to reduce episodic memory performance in healthy, young adults. These findings reaffirm that a more accurate explanation of cognitive variance can be achieved by looking at the synergistic effects of genotype and phenotype factors." [161]

1.12 Gene Tested: Mu Opioid Receptor (OPRM1)

Pharmacogenetics of OPRM1.
http://www.ncbi.nlm.nih.gov/pubmed/24201053/ [162]

"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." [162]

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 [163]

"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." [163]

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

http://www.ncbi.nlm.nih.gov/pubmed/25809606 [164]

"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." [164]

The AC/AG Diplotype for the 118A>G and IVS2 + 691G>C Polymorphisms of OPRM1 Gene is Associated with Sleep Quality Among Opioid-Dependent Patients on Methadone Maintenance Therapy.

http://www.ncbi.nlm.nih.gov/pubmed/26792136 [165]

"Patients with IVS2 + 691 CC genotype had higher PSQI scores [mean (SD) = 5.73 (2.89)] compared to those without the IVS2 + 691 CC genotype (IVS2 + 691 GG/GC genotype) [4.92 (2.31)], but the difference did not reach statistical significance (p = 0.081). Patients with combined 118 AA genotype and IVS2 + 691 GC genotype (AC/AG diplotype) had significantly lower PSQI scores [mean (SD) = 4.25 (2.27)] compared to those without the diplotype [5.68 (2.77)] (p = 0.018)." [165]

The Influence of Genotype Polymorphism on Morphine Analgesic Effect for Postoperative Pain in Children.

http://www.ncbi.nlm.nih.gov/pubmed/26839669 [166]

"Children with at least one G allele for OPRM1 (AG/GG) had higher postoperative pain scores compared with those with the AA genotype at the time of discharge from the post-anesthesia care unit (P = 0.025). Other recovery profiles were not significantly different between the two groups. There was no significant relationship between genotypes and postoperative pain scores in analysis of ABCB1 and COMT polymorphisms. Genetic polymorphism at OPRM1 A118G, but not at ABCB1 C3435T and COMT Val158Met, influences the analgesic effect of morphine for immediate acute postoperative pain in children." [166]

The pharmacogenetics of opioid therapy in the management of postpartum pain: a systematic review.

http://www.ncbi.nlm.nih.gov/pubmed/26652709 [167]

"Among the 2082 papers retrieved from the search, 17 were included in the review. These 17 papers consisted of various study designs, opioids, polymorphisms and patient outcomes. This systematic review reveals that CYP2D6, OPRM1 A118G, UGT2B7 C802T and ABCB1 G2677AT may contribute to postpartum analgesia or adverse events." [167]

Variation in Mu-Opioid Receptor Gene (OPRM1) as a Moderator of Naltrexone Treatment to Reduce Heavy Drinking in a High Functioning Cohort.

https://www.ncbi.nlm.nih.gov/pubmed/24729984 [168]

"It is well known that naltrexone, an FDA-approved medication for treatment of alcohol dependence, is effective for only a subset of individuals. Recent studies have examined the utility of a functional A118G single nucleotide polymorphism (SNP) of the mu-opioid receptor gene (OPRM1) as a predictor of naltrexone treatment response. Although the findings to date have generally been consistent with a moderating effect of the SNP, further evaluation of this hypothesis is warranted…Naltrexone-treated subjects with one or two 118G alleles had a significantly greater percentage of non-hazardous drinking (NoH) (p < 0.01) than those treated with placebo or A118 homozygotes in

either medication group. These results are consistent with a modest moderating effect of the OPRM1 118G allele on the reduction of heavy drinking by naltrexone treatment." [168]

Variation in OPRM1 moderates the effect of desire to drink on subsequent drinking and its attenuation by naltrexone treatment.

https://www.ncbi.nlm.nih.gov/pubmed/22784013 [169]

"To evaluate the role of the functional Asn40Asp polymorphism in the mu-opioid receptor gene on drinking behavior and naltrexone's ability to attenuate drinking, we used a daily diary method in a 12-week, randomized clinical trial of naltrexone to reduce drinking. Participants (n = 158 problem drinkers) were assigned to receive either daily or targeted naltrexone 50 mg (n = 81) or matching placebo (n = 77)… In summary, when the evening level of desire to drink was relatively high, Asp40 allele carriers were at greater risk than Asn40 homozygotes to drink more, which was attenuated by naltrexone. Although average measures across the study were not informative, daily reports helped to demonstrate the moderating effects of genetic variation on the relation between desire to drink and alcohol consumption and the effects of naltrexone on that phenotype." [169]

Association of μ-opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: a systematic review and meta-analysis.

https://www.ncbi.nlm.nih.gov/pubmed/22515274 [170]

"Previous studies have suggested that the effect of naltrexone in patients with alcohol dependence may be moderated by genetic factors. In particular, the possession of the G allele of the A118G polymorphism of the micro-opioid receptor gene (OPRM1) has been associated with a better response to naltrexone, although controversial results have been reported. The aim of this paper is to combine previous findings by means of a systematic review and a meta-analysis. We retrieved studies on the relationship between A118G polymorphism in OPRM1 gene and response to treatment with naltrexone in patients with alcohol dependence by means of electronic database search. A meta-analysis was conducted using a random-effects model. Calculations of odds ratio (OR) and their confidence intervals (CI) and tests for heterogeneity of the results have been performed. Six previous studies have analyzed the role of A118G polymorphism in response to naltrexone for alcohol dependence. After meta-analysis, we found that naltrexone-treated patients carrying the G allele had lower relapse rates than those who were homozygous for the A allele (OR: 2.02, 95% CI 1.26-3.22; P = 0.003). There were no differences in abstinence rates. Our results support the fact that the G allele of A118G polymorphism of OPRM1 moderates the effect of naltrexone in patients with alcohol dependence. This genetic marker may therefore identify a subgroup of individuals more likely to respond to this treatment." [170]

A polymorphism of the mu-opioid receptor gene (OPRM1) and sensitivity to the effects of alcohol in humans.

https://www.ncbi.nlm.nih.gov/pubmed/15608594 [171]

"Recent research has implicated the endogenous opioid system in the development of alcohol use disorders. The A118G polymorphism of the OPRM1 gene has been shown to confer functional differences to mu-opioid receptors, such that the G variant binds beta-endorphin three times more strongly than the A variant. The goal of this study was to test whether the A118G polymorphism is associated with sensitivity to the effects of alcohol…These findings may help to explain previous research suggesting that naltrexone is more effective among individuals with the G allele. A medication that reduces feelings of euphoria after alcohol consumption may be more successful among individuals with a genetic predisposition to greater feelings of euphoria after consuming alcohol." [171]

An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study.

https://www.ncbi.nlm.nih.gov/pubmed/18250251 [172]

"Naltrexone hydrochloride treatment for alcohol dependence works for some individuals but not for everyone. Asn40Asp, a functional polymorphism of the mu-opioid receptor gene (OPRM1), might predict naltrexone response. To evaluate whether individuals with alcoholism who are heterozygous (Asp40/Asn40) or homozygous (Asp40/Asp40) for the OPRM1 Asp40 allele respond better to naltrexone…These results confirm and extend the observation that the functionally significant OPRM1 Asp40 allele predicts naltrexone treatment response in alcoholic individuals. This relationship might be obscured, however, by other efficacious treatments. OPRM1 genotyping in alcoholic individuals might be useful to assist in selecting treatment options." [172]

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 [173]

"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." [173]

Posttreatment effects of topiramate treatment for heavy drinking.
http://www.ncbi.nlm.nih.gov/pubmed/25581656 [174]

"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." [174]

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 [175]

"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. 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." [175]

Self-efficacy mediates the effects of topiramate and GRIK1 genotype on drinking.
http://www.ncbi.nlm.nih.gov/pubmed/25496338 [176]

"In a 12-week, placebo-controlled trial of topiramate, we used daily interactive voice response technology to measure self-efficacy (i.e. confidence in avoiding heavy drinking later in the day) and drinking behavior in 122 European-American heavy drinkers. Topiramate's effects on both self-efficacy and drinking level were moderated by rs2832407. C-allele homozygotes treated with topiramate showed higher levels of self-efficacy and lower levels of nighttime drinking across the 12-week trial. Further, the interactive effect of topiramate and genotype on mean nighttime drinking levels was mediated by mean levels of self-efficacy. By modeling topiramate's effects on nighttime drinking across multiple levels of analysis, we found that self-efficacy, a key psychologic construct, mediated the effect of topiramate, which was moderated by rs2832407 genotype. Thus, it may be possible to use an individualized assessment (i.e. genotype) to select treatment to optimize the reduction in heavy drinking and thereby provide a personalized treatment approach" [176]

Balancing risk and benefit in heavy drinkers treated with topiramate: implications for personalized care.
https://www.ncbi.nlm.nih.gov/pubmed/26891181 [177]

The number needed to treat (NNT) "for topiramate was 5.29, the NNT for patients with moderate adverse events was 7.52, and the NNT for patients with severe adverse events was 6.12. Among European Americans with the rs2832407*CC genotype, the NNT was 2.28, the NNT for patients with moderate adverse events was 2.63, and the NNT for patients with severe adverse events was 2.56. In contrast, for rs2832407*A-allele carriers, the NNT was 180.00, the NNT for patients with moderate adverse events was 322.16, and the NNT for patients with severe adverse events was 217.45…In this sample of heavy drinkers, topiramate had a clinically important treatment effect that was most evident in European Americans with the rs2832407*CC genotype. In that group, in particular, it had a robust treatment effect, even when adjusted for adverse events." [177]

Pharmacokinetic Genes

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

Pharmacogenetics of second-generation antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/24897292 [72]

The Human Cytochrome P450 (CYP) Allele Nomenclature Database.
http://www.cypalleles.ki.se/ [178]

PharmGKB The Pharmacogenomics Knowledgebase.
https://www.pharmgkb.org/ [179]

Clinical applications of CYP genotyping in psychiatry.
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [180]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects.
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [181]

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. [72, 178-181]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver.
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [182]

"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." [182]

CYP450 pharmacogenetic treatment strategies for antipsychotics: a review of the evidence.
http://www.ncbi.nlm.nih.gov/pubmed/23870808 [183]

"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." [183]

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 [184]

"To date, more than 15 variant alleles and a series of sub-variants 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 induction whereas *1C causes reduced induction. Further studies are warranted to explore the clinical and toxicological significance of altered CYP1A2 expression and activity caused by genetic, epigenetic, and environmental factors." [184]

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 [185]

"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." [185]

The Dosing of Atypical Antipsychotics.

http://www.ncbi.nlm.nih.gov/pubmed/15883149 [186]

"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." [186]

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

http://www.ncbi.nlm.nih.gov/pubmed/18466106 [187]

"CYP1A2 is involved in the metabolism of several widely used drugs and endogenous compounds, and in the activation of pro-carcinogens. 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." [187]

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

http://www.ncbi.nlm.nih.gov/pubmed/24464701 [188]

"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." [188]

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

http://www.ncbi.nlm.nih.gov/pubmed/14563787 [189]

"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." [189]

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

http://www.ncbi.nlm.nih.gov/pubmed/22901441 [190]

"CYP1A2 *1F contains a 163 C4A transition in intron 1, which influences the gene's induction 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 characterized. CYP1A2 *1C contains a 3860 G>A transition in the flanking region of the gene, causing a decrease in induction. CYP1A2 *1F contains a 163 C>A transition in intron 1, which influences gene induction 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)." [190]

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 [191]

"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." [191]

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 [192]

"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-->Del T 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." [192]

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

http://www.ncbi.nlm.nih.gov/pubmed/23859573 [193]

"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." [193]

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

http://www.ncbi.nlm.nih.gov/pubmed/19636338 [194]

"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." [194]

Genetics of caffeine consumption and responses to caffeine.

http://www.ncbi.nlm.nih.gov/pubmed/20532872 [195]

"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 induction of the P-450 1A2 enzyme in Caucasian subjects. 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." [195]

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

http://www.ncbi.nlm.nih.gov/pubmed/12445035 [196]

"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." [196]

CYP1A2, GSTM1, and GSTT1 polymorphisms and diet effects on CYP1A2 activity in a crossover feeding trial.

http://www.ncbi.nlm.nih.gov/pubmed/19843669 [197]

"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." [197]

Duloxetine: clinical pharmacokinetics and drug interactions.
http://www.ncbi.nlm.nih.gov/pubmed/21366359 [198]

"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) of duloxetine 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." [198]

Genomics and pharmacogenomics of schizophrenia.
http://www.ncbi.nlm.nih.gov/pubmed/20718829 [199]

"Schizophrenia (SCZ) is among the most disabling of mental disorders…SCZ has a heritability estimated at 60-90%. Genetic studies in SCZ have revealed the presence of chromosome anomalies, copy number variants, multiple single-nucleotide polymorphisms of susceptibility distributed across the human genome, aberrant single nucleotide polymorphisms (SNPs) in microRNA genes, mitochondrial DNA mutations, and epigenetic phenomena. Pharmacogenetic studies of psychotropic drug response have focused on determining the relationship between variation in specific candidate genes and the positive and adverse effects of drug treatment. Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and 95% of CYP3A4. About 10-20% of Western populations are defective in genes of the CYP superfamily. Only 26% of Southern Europeans are pure extensive metabolizers for the tri-genic cluster integrated by the CYP2D6+CYP2C19+CYP2C9 genes. The pharmacogenomic response of SCZ patients to conventional psychotropic drugs also depends on genetic variants associated with SCZ-related genes. Consequently, the incorporation of pharmacogenomic procedures both to drugs in development and drugs on the market would help to optimize therapeutics in SCZ and other central nervous system (CNS) disorders." [199]

Pharmacogenomics can improve antipsychotic treatment in schizophrenia.
http://www.ncbi.nlm.nih.gov/pubmed/23606027 [200]

"Schizophrenia is a widespread mental disease with a prevalence of about 1% in the world population, and heritability of up to 80%. Drug therapy is an important approach to treating the disease. However, the curative effect of antipsychotic is far from satisfactory in terms of tolerability and side effects. Many studies have indicated that nearly 30% of patients exhibit little or no improvements associated with antipsychotics. The response of individual patients who are given the same dose of the same drug varies considerably. In addition, antipsychotic drugs are often accompanied by adverse drug reactions (ADRs), which can cause considerable financial loss in addition to the obvious societal harm… In this review, we will focus on the latest research on polymorphisms of candidate genes that code for drug metabolic enzymes (CYP2D6, CYP1A2, CYP3A4, etc.), drug transporters (mainly ABCB1) and neurotransmitter receptors (dopamine receptors and serotonin receptors, etc.). We also discuss the genome-wide pharmacogenomic study of schizophrenia and review the current state of knowledge on epigenetics and potential clinical applications." [200]

The CYP1A2 -163C>A polymorphism is associated with clozapine-induced generalized tonic-clonic seizures in Brazilian schizophrenia patients.
http://www.ncbi.nlm.nih.gov/pubmed/23601795 [201]

"We evaluated two polymorphisms at CYP1A2 (*1C and *1F) in a sample of 108 European-derived patients with schizophrenia and their influence on the pro-convulsive effect of clozapine. We found the *1F/*1F genotype to be significantly associated with seizures, and no relationship was observed with combinations of *1F and *1C alleles." [201]

Clinically significant drug interactions with atypical antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/24170642 [202]

"Atypical antipsychotics [also known as second-generation antipsychotics (SGAs)] have become a mainstay therapeutic treatment intervention for patients with schizophrenia, bipolar disorders and other psychotic conditions. … Smoking is very common among psychiatric patients and can induce CYP1A2 enzymes, thereby lowering expected plasma levels of certain SGAs. It is recommended that ziprasidone and lurasidone are taken with food to promote drug absorption, otherwise their bioavailability can be reduced. Clinicians must be aware of the variety of factors that can increase the likelihood of clinically significant drug interactions with SGAs, and must carefully monitor patients to maximize treatment efficacy while minimizing adverse events." [202]

Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions.
http://www.ncbi.nlm.nih.gov/pubmed/25987241 [203]

"We evaluated the cost-effectiveness of one-time pharmacogenomic testing for preventing adverse drug reactions (ADRs) over a patient's lifetime. We developed a Markov-based Monte Carlo microsimulation model to represent the ADR events in the lifetime of each patient. The base-case considered a 40-year-old patient. We measured health outcomes in life years (LYs) and quality-adjusted LYs (QALYs) and estimated costs using 2013 US$. In the base-case, one-time genetic testing had an incremental cost-effectiveness ratio (ICER) of $43,165 (95% confidence interval (CI) is ($42, 769, $43,561)) per additional LY and $53,680 per additional QALY (95% CI is ($53, 182, $54,179)), hence under the base-case one-time genetic testing is cost-effective. The ICER values were most sensitive to the average probability of death due to ADR, reduction in ADR rate due to genetic testing, mean ADR rate and cost of genetic testing." [203]

Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: a systematic review.
https://www.ncbi.nlm.nih.gov/pubmed/24160757 [204]

"Exogenous cannabinoids are structurally and pharmacologically diverse compounds that are widely used. The purpose of this systematic review is to summarize the data characterizing the potential for these compounds to act as substrates, inhibitors, or inducers of human drug metabolizing enzymes, with the aim of clarifying the significance of these properties in clinical care and drug interactions… However, the absence of interaction between CBD from oromucosal cannabis extract with omeprazole suggests a less significant role of CYP2C19 in CBD metabolism. Studies of THC, CBD, and CBN inhibition and induction of major human CYP-450 isoforms generally reflect a low risk of clinically significant drug interactions with most use, but specific human data are lacking. Smoked cannabis herb (marijuana) likely induces CYP1A2 mediated theophylline metabolism, although the role of cannabinoids specifically in eliciting this effect is questionable." [204]

Cruciferous vegetable consumption alters the metabolism of the dietary carcinogen 2-amino-1-methyl-6-phenylimidazo [4, 5-b] pyridine (PhIP) in humans.
https://www.ncbi.nlm.nih.gov/pubmed/15073045 [205]

"Consumption of red meat is associated with an increased risk of colorectal cancer, whereas cruciferous vegetable consumption reduces cancer risk. While the mechanisms remain to be determined, cruciferous vegetables may act by altering the metabolism of carcinogens present in cooked food, such as the heterocyclic amine 2-amino-1-methyl-6-phenylimidazo [4, 5-b] pyridine (PhIP). The aim of this study was to evaluate the effect of cruciferous vegetable consumption on the metabolism of PhIP in 20 non-smoking Caucasian male subjects…While the urinary excretion of both PhIP metabolites accounted for approximately 39% of the PhIP dose in phases 1 and 3, they accounted for approximately 49% of the dose in phase 2. This study demonstrates that cruciferous vegetable consumption can induce both the phase I and II metabolism of PhIP in humans." [205]

Genetic polymorphism analysis of the drug-metabolizing enzyme CYP1A2 in a Uyghur Chinese population: a pilot study.
https://www.ncbi.nlm.nih.gov/pubmed/26383175 [206]

"CYP1A2 is a highly polymorphic gene and CYP1A2 enzyme results in broad inter-individual variability in response to certain pharmacotherapies, while little is known about the genetic variation of CYP1A2 in Uyghur Chinese population. The aim of the present study was to screen Uyghur volunteers for CYP1A2 genetic polymorphisms. 2. We used DNA sequencing to investigate promoter, exons, introns, and 3' UTR of the CYP1A2 gene in 96 unrelated healthy Uyghur individuals. We also used SIFT (Sorting Intolerant from Tolerant) and PolyPhen-2 (Polymorphism Phenotyping v2) to predict the protein function of the novel non-synonymous mutation in CYP1A2 coding regions. 3. We identified 20 different CYP1A2 polymorphisms in the Uyghur Chinese population, including two novel variants (119A > G and 2410G > A). Variant 119A > G was predicted to be probably damaging on protein function by PolyPhen-2, by contrast, 2410G > A was identified as benign. The allele frequencies of CYP1A2*1A, *1B, *1F, *1G, *1J, *1M, *4, and *9 were 23.4%, 53.1%, 3.7%, 2.6%, 2.6%, 13.5%, 0.5%, and 0.5%, respectively. The frequency of *1F, a highly inducible allele, was higher in our sample population compared with that in the Caucasian population ($p < 0.05$). The most common genotype combinations were *1A/*1B (46.9%) and *1B/*1M (27.1%). 4. Our results provide basic information on CYP1A2 polymorphisms in Uyghur individuals and suggest that the enzymatic activities of CYP1A2 may differ among the diverse ethnic populations of the world." [206]

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

The Human Cytochrome P450 (CYP) Allele Nomenclature Database.
http://www.cypalleles.ki.se/ [178]

PharmGKB The Pharmacogenomics Knowledgebase.
https://www.pharmgkb.org/ [179]

Clinical applications of CYP genotyping in psychiatry.
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [180]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects.
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [181]

Applications of CYP450 testing in the clinical setting.
http://www.ncbi.nlm.nih.gov/pubmed/23588782 [207]

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. [178-180, 207]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver.
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [182]

"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." [182]

Pharmacogenetics of cytochrome P450 2B6 (CYP2B6): advances on polymorphisms, mechanisms, and clinical relevance.
http://www.ncbi.nlm.nih.gov/pubmed/23467454 [208]

CYP2B6: New Insights into a Historically Overlooked Cytochrome P450 Isozyme.
http://www.ncbi.nlm.nih.gov/pubmed/18781911 [209]

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. [208-209]

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 [210]

"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." [210]

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/pubmed/21659470 [211]

"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." [211]

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 [212]

"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 analyzing 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." [212]

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 [213]

"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." [213]

Impact of CYP2B6 polymorphism on hepatic efavirenz metabolism in vitro.
http://www.ncbi.nlm.nih.gov/pubmed/17559344 [214]

"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." [214]

CYP2B6 SNPs are associated with methadone dose required for effective treatment of opioid addiction.
http://www.ncbi.nlm.nih.gov/pubmed/21790905 [215]

"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." [215]

Genomics and pharmacogenomics of schizophrenia.
http://www.ncbi.nlm.nih.gov/pubmed/20718829 [199]

"Schizophrenia (SCZ) is among the most disabling of mental disorders…SCZ has a heritability estimated at 60-90%. Genetic studies in SCZ have revealed the presence of chromosome anomalies, copy number variants, multiple single-nucleotide polymorphisms of susceptibility distributed across the human genome, aberrant single nucleotide polymorphisms (SNPs) in microRNA genes, mitochondrial DNA mutations, and epigenetic phenomena. Pharmacogenetic studies of psychotropic drug response have focused on determining the relationship between variation in specific candidate genes and the positive and adverse effects of drug treatment. Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and 95% of CYP3A4. About 10-20% of Western populations are defective in genes of the CYP superfamily. Only 26% of Southern Europeans are pure extensive metabolizers for the tri-genic cluster integrated by the CYP2D6+CYP2C19+CYP2C9 genes. The pharmacogenomic response of SCZ patients to conventional psychotropic drugs also depends on genetic variants associated with SCZ-related genes. Consequently, the incorporation of pharmacogenomic procedures both to drugs in development and drugs on the market would help to optimize therapeutics in SCZ and other central nervous system (CNS) disorders." [199]

Pharmacogenomics study in a Taiwan methadone maintenance cohort.
http://www.ncbi.nlm.nih.gov/pubmed/25278738 [216]

"Pharmacogenomics is research to study the drug treatment responses in subgroups of patients according to their genetic variants or genetic expression information. Methadone maintenance treatment, which is usually prescribed for patients with heroin dependence, was launched in Taiwan by the government in 2006. In this study, 366 patients who had taken methadone continually in the previous 7 days were examined. Data from administration of the Treatment Outcomes Profile (TOP), Severity of Dependence Scale (SDS), Clinical Opioid Withdrawal Scale (COWS), and Treatment Emergent Symptoms Scale (TESS) were obtained from patients' report records. Genes encoding the liver cytochrome P-450 (CYP) enzymes that are involved with the metabolism of methadone (CYP2B6, 3A4 and 2C19) were selected and genotyped in this cohort. We found that the SNPs on CYP2B6 were associated with plasma S-methadone concentration; SNPs on CYP3A4 were associated with withdrawal symptoms and side effects; and SNPs on CYP2C19 were associated with methadone dose. SNPs in the genes encoding the morphine phase II metabolic enzyme, UGT2B7, were associated with withdrawal symptom scores. In pharmacodynamic genes, the SNPs on OPRM1 were associated with insomnia and change in libido side effects. We conclude that SNP markers may be useful for future methadone dosage adjustment and to reduce adverse reactions." [216]

Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions.
http://www.ncbi.nlm.nih.gov/pubmed/25987241 [203]

"We evaluated the cost-effectiveness of one-time pharmacogenomic testing for preventing adverse drug reactions (ADRs) over a patient's lifetime. We developed a Markov-based Monte Carlo microsimulation model to represent the ADR events in the lifetime of each patient. The base-case considered a 40-year-old patient. We measured health outcomes in life years (LYs) and quality-adjusted LYs (QALYs) and estimated costs using 2013 US$. In the base-case, one-time genetic testing had an incremental cost-effectiveness ratio (ICER) of $43,165 (95% confidence interval (CI) is ($42, 769, $43,561)) per additional LY and $53,680 per additional QALY (95% CI is ($53, 182, $54,179)), hence under the base-case one-time genetic testing is cost-effective. The ICER values were most sensitive to the average probability of death due to ADR, reduction in ADR rate due to genetic testing, mean ADR rate and cost of genetic testing." [203]

CYP2B6 and bupropion's smoking-cessation pharmacology: the role of hydroxybupropion.
https://www.ncbi.nlm.nih.gov/pubmed/23149928 [217]

"Bupropion is indicated to promote smoking cessation. Animal studies suggest that the pharmacologic activity of bupropion can be mediated by its major metabolite, hydroxybupropion. We measured plasma bupropion and its metabolite levels in a double-blind, placebo controlled, randomized smoking-cessation trial…These findings suggest that dosing of bupropion to achieve a hydroxybupropion level of 0.7 μg/ml or increasing bupropion dose for CYP2B6 slow metabolizers could improve bupropion's cessation outcomes." [217]

Serum concentrations of hydroxybupropion for dose optimization of depressed patients treated with bupropion.
https://www.ncbi.nlm.nih.gov/pubmed/24452068 [218]

"Bupropion is a dopamine and norepinephrine reuptake inhibitor approved for the treatment of depression and smoking cessation. According to the recently published reviews, it is a candidate for therapeutic drug monitoring (TDM) to improve therapeutic outcomes and reduce risks of intolerability or intoxication. In practice, however, the use of TDM is limited due to the chemical instability of bupropion. This investigation sought to determine if the major, active, and chemically stable metabolite 4-hydroxybupropion is a suitable measure to guide antidepressant drug therapy with bupropion…Despite multiple limitations of this naturalistic study, evidence could be given that the measurement of 4-hydroxybupropion in serum is suitable to perform TDM for bupropion. Blood levels should be above 860 ng/mL to attain therapeutic improvement. Potential sex differences in bupropion pharmacokinetics, probably due to differential activities of CYP2B6, should be taken into account when the drug is prescribed." [218]

A simple and sensitive LC-ESI-MS (ion trap) method for the determination of bupropion and its major metabolite, hydroxybupropion in rat plasma and brain microdialysates.
https://www.ncbi.nlm.nih.gov/pubmed/21315892 [219]

"A specific and highly sensitive liquid chromatography-electrospray mass spectrometry (LC-ESI-MS) method for the direct determination of bupropion (BUP) and its main metabolite hydroxybupropion (HBUP) in rat plasma and brain microdialysate has been developed and validated. The analysis was performed on a Bonus RP C18 (100 mm × 2.1mm i.d., 3.5 μm particles) column using gradient elution with the mobile phase consisting of acetonitrile and ammonium formate buffer (10mM, pH 4)…The method was validated in both plasma and microdialysate samples, and the obtained lower limit of quantification (LLOQ) was 1.5 ng mL (-1) for BUP and HBUP in both matrices. The intra- and inter-day assay variability was less than 15% for both analytes. This LC-ESI-MS method provided simple sampling, rapid clean-up and short analysis time (<9 min), applicable to the routine therapeutic monitoring and pharmacokinetic studies of BUP and HBUP." [219]

Effect of CYP2B6*6 on Steady-State Serum Concentrations of Bupropion and Hydroxybupropion in Psychiatric Patients: A Study Based on Therapeutic Drug Monitoring Data.
https://www.ncbi.nlm.nih.gov/pubmed/25565674 [220]

"The clinical effect of bupropion is mediated by its active metabolite hydroxybupropion. Previous studies have reported conflicting impact of the CYP2B6*6 variant allele on the formation of hydroxybupropion from bupropion. The aim of this study was to clarify the effect of CYP2B6*6 and secondarily CYP2D6 genotype on steady-state serum concentrations of bupropion and hydroxybupropion in a large population of psychiatric patients…This study shows that the CYP2B6*6 variant allele is associated with significantly reduced formation of the active bupropion metabolite in psychiatric patients. Our findings suggest that dose-adjusted serum concentrations of hydroxybupropion at steady state is approximately halved in homozygous CYP2B6*6 carriers, which might imply risk of reduced clinical response in this patient subgroup. The CYP2D6 genotype does not affect hydroxybupropion concentrations and is therefore unlikely to impact bupropion treatment." [220]

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

The Human Cytochrome P450 (CYP) Allele Nomenclature Database.
http://www.cypalleles.ki.se/ [178]
PharmGKB The Pharmacogenomics Knowledgebase.
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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 [182]

"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." [182]

The Dosing of Atypical Antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/15883149 [186]

"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." [186]

Cytochrome P450 2C9-CYP2C9.
http://www.ncbi.nlm.nih.gov/pubmed/20150829 [221]

"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." [221]

Pharmacogenetics: From Bench to Byte— An Update of Guidelines.
http://www.ncbi.nlm.nih.gov/pubmed/21412232 [222]

"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)." [222]

Characterization of 107 Genomic DNA Reference Materials for *CYP2D6*, *CYP2C19*, *CYP2C9*, *VKORC1*, and *UGT1A1*.
http://www.ncbi.nlm.nih.gov/pubmed/20889555 [223]

"[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." [223]

Drug metabolizing enzyme activities versus genetic variances for drug of clinical pharmacogenomic relevance.
http://www.ncbi.nlm.nih.gov/pubmed/21906384 [224]

"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." [224]

Polymorphisms of human cytochrome P450 2C9 and the functional relevance.
http://www.ncbi.nlm.nih.gov/pubmed/19715737 [225]

"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." [225]

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 [226]

"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." [226]

Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing.
http://www.ncbi.nlm.nih.gov/pubmed/21900891 [227]

"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 non-genetic factors, account for ~50% of warfarin dose variability." [227]

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 [228]

"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." [228]

Decreased warfarin clearance associated with the CYP2C9 R150H (*8) polymorphism.
http://www.ncbi.nlm.nih.gov/pubmed/22378156 [229]

"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." [229]

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 [230]

"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." [230]

Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options.
http://www.ncbi.nlm.nih.gov/pubmed/24523097 [231]

"Advancements in pharmacogenomics have introduced an increasing number of opportunities to bring personalized medicine into clinical practice. Understanding how and when to use this technology to guide pharmacotherapy used to treat psychiatric and neurological (neuropsychiatric) conditions remains a challenge for many clinicians. Currently, guidelines exist to assist clinicians in the use of existing genetic information for drug selection and/or dosing for the tricyclic antidepressants, carbamazepine, and phenytoin. Additional language in the product labeling suggests that genetic information may also be useful for determining the starting and target doses, as well as drug interaction potential, for a number of other drugs. In this review, we outline the current status of pharmacogenomic testing for neuropsychiatric drugs as it pertains to information contained in drug labeling, consensus guidelines, and test panels, as well as considerations related to obtaining tests for patients." [231]

Role of cytochrome P450 genotype in the steps toward personalized drug therapy.
http://www.ncbi.nlm.nih.gov/pubmed/23226058 [232]

"Genetic polymorphism for cytochrome 450 (P450) enzymes leads to interindividual variability in the plasma concentrations of many drugs. In some cases, P450 genotype results in decreased enzyme activity and an increased risk for adverse drug effects…The CYP2C9, CYP2C19, and CYP2D6 genes are the P450 genes most often cited. To date, integration of P450 genetic information into clinical decision making is limited. However, some institutions are beginning to embrace routine P450 genotyping to assist in the treatment of their patients. Genotyping for P450 variants may carry less risk for discrimination compared with genotyping for disease-associated variants. As such, P450 genotyping is likely to lead the way in the clinical implementation of pharmacogenomics. This review discusses variability in the CYP2C9, CYP2C19, and CYP2D6 genes and the implications of this for drug efficacy and safety." [232]

Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions.
http://www.ncbi.nlm.nih.gov/pubmed/25987241 [203]

"We evaluated the cost-effectiveness of one-time pharmacogenomic testing for preventing adverse drug reactions (ADRs) over a patient's lifetime. We developed a Markov-based Monte Carlo microsimulation model to represent the ADR events in the lifetime of each patient. The base-case considered a 40-year-old patient. We measured health outcomes in life years (LYs) and quality-adjusted LYs (QALYs) and estimated costs using 2013 US$. In the base-

case, one-time genetic testing had an incremental cost-effectiveness ratio (ICER) of $43,165 (95% confidence interval (CI) is ($42, 769, $43,561)) per additional LY and $53,680 per additional QALY (95% CI is ($53, 182, $54,179)), hence under the base-case one-time genetic testing is cost-effective. The ICER values were most sensitive to the average probability of death due to ADR, reduction in ADR rate due to genetic testing, mean ADR rate and cost of genetic testing." [203]

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/ [178]

PharmGKB The Pharmacogenomics Knowledgebase.
https://www.pharmgkb.org/ [179]

Clinical applications of CYP genotyping in psychiatry.
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [180]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects.
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [181]

Applications of CYP450 testing in the clinical setting.
http://www.ncbi.nlm.nih.gov/pubmed/23588782 [207]

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. [7,178-181, 207]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver.
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [182]

"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." [182]

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 [233]

"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)." [233]

Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants.
http://www.ncbi.nlm.nih.gov/pubmed/23486447 [234]

"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." [234]

Pharmacogenetics: From Bench to Byte— An Update of Guidelines.
http://www.ncbi.nlm.nih.gov/pubmed/21412232 [222]

"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)." [222]

Characterization of 107 Genomic DNA Reference Materials for *CYP2D6*, *CYP2C19*, *CYP2C9*, *VKORC1*, and *UGT1A1*.
http://www.ncbi.nlm.nih.gov/pubmed/20889555 [223]

"[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." [223]

Drug metabolizing enzyme activities versus genetic variances for drug of clinical pharmacogenomic relevance.
http://www.ncbi.nlm.nih.gov/pubmed/21906384 [224]

"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." [224]

Metabolic ratios of psychotropics as indication of cytochrome P450 2D6/2C19 genotype.
http://www.ncbi.nlm.nih.gov/pubmed/16044105 [235]

"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." [235]

CYP2C19 variation and citalopram response.
http://www.ncbi.nlm.nih.gov/pubmed/21192344 [236]

"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." [236]

Impact of the Ultrarapid CYP2C19*17 Allele on Serum Concentration of Escitalopram in Psychiatric Patients.
http://www.ncbi.nlm.nih.gov/pubmed/17625515 [237]

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 [238]

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 [239]

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 [240]

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 ultra rapid metabolism of CYP2C19 substrates, producing lower plasma levels of drugs and probable decreases in efficacy. [237-240]

Influence of CYP2D6 and CYP2C19 genotypes on venlafaxine metabolic ratios and stereo selective metabolism in forensic autopsy cases.

http://www.ncbi.nlm.nih.gov/pubmed/25245581 [241]

"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 favors the R-enantiomer whereas CYP2C19 favors the S-enantiomer." [241]

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

http://www.ncbi.nlm.nih.gov/pubmed/25001882 [242]

"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." [242]

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 [243]

"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." [243]

Genomics and pharmacogenomics of schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/20718829 [199]

"Schizophrenia (SCZ) is among the most disabling of mental disorders…SCZ has a heritability estimated at 60-90%. Genetic studies in SCZ have revealed the presence of chromosome anomalies, copy number variants, multiple single-nucleotide polymorphisms of susceptibility distributed across the human genome, aberrant single nucleotide polymorphisms (SNPs) in microRNA genes, mitochondrial DNA mutations, and epigenetic phenomena. Pharmacogenetic studies of psychotropic drug response have focused on determining the relationship between variation in specific candidate genes and the positive and adverse effects of drug treatment. Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and 95% of CYP3A4. About 10-20% of Western populations are defective in genes of the CYP superfamily. Only 26% of Southern Europeans are pure extensive metabolizers for the tri-genic cluster integrated by the CYP2D6+CYP2C19+CYP2C9 genes. The pharmacogenomic response of SCZ patients to conventional psychotropic drugs also depends on genetic variants associated with SCZ-related genes. Consequently, the incorporation of pharmacogenomic procedures both to drugs in development and drugs on the market would help to optimize therapeutics in SCZ and other central nervous system (CNS) disorders." [199]

Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options.

http://www.ncbi.nlm.nih.gov/pubmed/24523097 [231]

"Advancements in pharmacogenomics have introduced an increasing number of opportunities to bring personalized medicine into clinical practice. Understanding how and when to use this technology to guide pharmacotherapy used to treat psychiatric and neurological (neuropsychiatric) conditions remains a challenge for many clinicians. Currently, guidelines exist to assist clinicians in the use of existing genetic information for drug selection and/or dosing for the tricyclic antidepressants, carbamazepine, and phenytoin. Additional language in the product labeling suggests that genetic information may also be useful for determining the starting and target doses, as well as drug interaction potential, for a number of other drugs. In this review, we outline the current status of pharmacogenomic testing for neuropsychiatric drugs as it pertains to information contained in drug labeling, consensus guidelines, and test panels, as well as considerations related to obtaining tests for patients." [231]

Role of cytochrome P450 genotype in the steps toward personalized drug therapy.

http://www.ncbi.nlm.nih.gov/pubmed/23226058 [232]

"Genetic polymorphism for cytochrome 450 (P450) enzymes leads to interindividual variability in the plasma concentrations of many drugs. In some cases, P450 genotype results in decreased enzyme activity and an increased risk for adverse drug effects. For example, individuals with the CYP2D6 loss-of-function genotype are at increased risk for ventricular arrhythmia if treated with usual does of thioridazine. In other cases, P450 genotype may influence the dose of a drug required to achieve a desired effect. This is the case with warfarin, with lower doses often necessary in carriers of a variant CYP2C9*2 or *3 allele to avoid supra-therapeutic anticoagulation. When a prodrug, such as clopidogrel or codeine, must undergo hepatic biotransformation to its active form, a loss-of-function P450 genotype leads to reduced concentrations of the active drug and decreased drug efficacy. In contrast, patients with multiple CYP2D6 gene copies are at risk for opioid-related toxicity if treated with usual doses of codeine-containing analgesics. At least 25 drugs contain information in their US Food and Drug Administration-approved labeling regarding P450 genotype. The CYP2C9, CYP2C19, and CYP2D6 genes are the P450 genes most often cited. To date, integration of P450 genetic information into clinical decision making is limited. However, some institutions are beginning to embrace routine P450 genotyping to assist in the treatment of their patients. Genotyping for P450 variants may carry less risk for discrimination compared with genotyping for disease-associated variants. As such, P450 genotyping is likely to lead the way in the clinical implementation of pharmacogenomics. This review discusses variability in the CYP2C9, CYP2C19, and CYP2D6 genes and the implications of this for drug efficacy and safety." [232]

Pharmacogenomics study in a Taiwan methadone maintenance cohort.

http://www.ncbi.nlm.nih.gov/pubmed/25278738 [216]

"Pharmacogenomics is research to study the drug treatment responses in subgroups of patients according to their genetic variants or genetic expression information. Methadone maintenance treatment, which is usually prescribed for patients with heroin dependence, was launched in Taiwan by the government in 2006. In this study, 366 patients who had taken methadone continually in the previous 7 days were examined. Data from administration of the Treatment Outcomes Profile (TOP), Severity of Dependence Scale (SDS), Clinical Opioid Withdrawal Scale (COWS), and Treatment Emergent Symptoms Scale (TESS) were obtained from patients' report records. Genes encoding the liver cytochrome P-450 (CYP) enzymes that are involved with the metabolism of methadone (CYP2B6, 3A4 and 2C19) were selected and genotyped in this cohort. We found that the SNPs on CYP2B6 were associated with plasma S-methadone concentration; SNPs on CYP3A4 were associated with withdrawal symptoms and side effects; and SNPs on CYP2C19 were associated with methadone dose. SNPs in the genes encoding the morphine phase II metabolic enzyme, UGT2B7, were associated with withdrawal symptom scores. In pharmacodynamic genes, the SNPs on OPRM1 were associated with insomnia and change in libido side effects. We conclude that SNP markers may be useful for future methadone dosage adjustment and to reduce adverse reactions." [216]

Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions.

http://www.ncbi.nlm.nih.gov/pubmed/25987241 [203]

"We evaluated the cost-effectiveness of one-time pharmacogenomic testing for preventing adverse drug reactions (ADRs) over a patient's lifetime. We developed a Markov-based Monte Carlo microsimulation model to represent the ADR events in the lifetime of each patient. The base-case considered a 40-year-old patient. We measured health outcomes in life years (LYs) and quality-adjusted LYs (QALYs) and estimated costs using 2013 US$. In the base-case, one-time genetic testing had an incremental cost-effectiveness ratio (ICER) of $43,165 (95% confidence interval (CI) is ($42, 769, $43,561)) per additional LY and $53,680 per additional QALY (95% CI is ($53, 182, $54,179)), hence under the base-case one-time genetic testing is cost-effective. The ICER values were most sensitive to the average probability of death due to ADR, reduction in ADR rate due to genetic testing, mean ADR rate and cost of genetic testing." [203]

Pharmacokinetic Pharmacogenetic Prescribing Guidelines for Antidepressants: A Template for Psychiatric Precision Medicine.

http://www.ncbi.nlm.nih.gov/pubmed/27289413 [244]

"Antidepressants are commonly prescribed medications in the United States, and there is increasing interest in individualizing treatment selection for more than 20 US Food and Drug Administration-approved treatments for major depressive disorder. Providing greater precision to pharmacotherapeutic recommendations for individual patients beyond the large-scale clinical trials evidence base can potentially reduce adverse effect toxicity profiles and increase response rates and overall effectiveness. It is increasingly recognized that genetic variation may contribute to this differential risk to benefit ratio and thus provides a unique opportunity to develop pharmacogenetic guidelines for psychiatry. Key studies and concepts that review the rationale for cytochrome P450 2D6 (CYP2D6) and cytochrome P450 2C19 (CYP2C19) genetic testing can be delineated by serum levels, adverse events, and clinical outcome measures (e.g, antidepressant response). In this article, we report the evidence that contributed to the implementation of pharmacokinetic pharmacogenetic guidelines for antidepressants primarily metabolized by CYP2D6 and CYP2C19." [244]

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 [72]

The Human Cytochrome P450 (CYP) Allele Nomenclature Database
.http://www.cypalleles.ki.se [178]

PharmGKB The Pharmacogenomics Knowledgebase.
https://www.pharmgkb.org/ [179]

Clinical applications of CYP genotyping in psychiatry.
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [180]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects.
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [181]

Applications of CYP450 testing in the clinical setting.
http://www.ncbi.nlm.nih.gov/pubmed/23588782 [207]

Polymorphism of Human Cytochrome P450 2D6 and Its Clinical Significance: Part I.
http://www.ncbi.nlm.nih.gov/pubmed/19817501 [245]

Polymorphism of Human Cytochrome P450 2D6 and Its Clinical Significance: Part II.
http://www.ncbi.nlm.nih.gov/pubmed/19902987 [246]

Recent examples on the clinical relevance of the CYP2D6 polymorphism and endogenous functionality of CYP2D6.
http://www.ncbi.nlm.nih.gov/pubmed/24088607 [247]

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 [248]

The CYP2D6 poor metabolizer phenotype may be associated with risperidone adverse drug reactions and discontinuation.
http://www.ncbi.nlm.nih.gov/pubmed/15669884 [249]

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, 72, 178-181, 210, 247-249]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver.
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [182]

"…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." [182]

CYP450 pharmacogenetic treatment strategies for antipsychotics: a review of the evidence.
http://www.ncbi.nlm.nih.gov/pubmed/23870808 [183]

"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." [183]

The Dosing of Atypical Antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/15883149 [186]

"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." [186]

Pharmacogenetics: From Bench to Byte— An Update of Guidelines.
http://www.ncbi.nlm.nih.gov/pubmed/21412232 [222]

"[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)." [222]

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 [250]

"Codeine is biologically converted 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 ultra rapid 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." [250]

Characterization of 107 Genomic DNA Reference Materials for *CYP2D6*, *CYP2C19*, *CYP2C9*, *VKORC1*, and *UGT1A1*.
http://www.ncbi.nlm.nih.gov/pubmed/20889555 [223]

"[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." [223]

Drug metabolizing enzyme activities versus genetic variances for drug of clinical pharmacogenomic relevance.
http://www.ncbi.nlm.nih.gov/pubmed/21906384 [224]

"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." [224]

Metabolic ratios of psychotropics as indication of cytochrome P450 2D6/2C19 genotype.
http://www.ncbi.nlm.nih.gov/pubmed/16044105 [235]

"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." [235]

CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure.
http://www.ncbi.nlm.nih.gov/pubmed/17301689 [251]

"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." [251]

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 [252]

"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." [252]

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 [253]

"Compared with PMs, EMs had significantly greater mean changes from baseline on 4 of 5 depression rating scales (all 4 comparisons, P ≤ .020). A significantly greater percentage of EMs achieved response or remission by most measures compared with PMs (4 of 5 comparisons, P ≤ .015). Rates of discontinuation and AEs did not differ significantly between EMs and PMs." [253]

Clinical Pharmacokinetics of Atomoxetine.
http://www.ncbi.nlm.nih.gov/pubmed/15910008 [254]

Effects of the CYP2D6*10 allele on the pharmacokinetics of atomoxetine and its metabolites.
http://www.ncbi.nlm.nih.gov/pubmed/26254792 [255]

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 [256]

Several studies have shown that CYP2D6 polymorphism can lead to altered 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. Poor metabolizers had higher frequencies of dry mouth, erectile dysfunction, hyperhidrosis, insomnia, and urinary retention compared with the other metabolizer groups. [254-256]

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 [257]

"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." [257]

Genetics-Based Population Pharmacokinetics and Pharmacodynamics of Risperidone in a Psychiatric Cohort.
http://www.ncbi.nlm.nih.gov/pubmed/26129906 [258]

"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." [258]

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 [259]

"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." [259]

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

http://www.ncbi.nlm.nih.gov/pubmed/25998998 [260]

"This review will focus specifically on CYP2D6 genetic polymorphisms and their relevance for poisoning due to amphetamines, opioid analgesics and antidepressants in humans…Either poor or extensive/ultra-rapid CYP2D6 metabolizers may be exposed to toxic effects of amphetamines, opioid analgesics and antidepressants. In these three categories, the level of evidence is substance dependent, with differences within the same pharmacological class." [260]

Opioid metabolism.

http://www.ncbi.nlm.nih.gov/pubmed/19567715 [261]

"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." [261]

CYP2D6 phenotype-specific codeine population pharmacokinetics.

http://www.ncbi.nlm.nih.gov/pubmed/25562725 [262]

"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 ultra rapid-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." [262]

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

http://www.ncbi.nlm.nih.gov/pubmed/25621429 [263]

"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." [263]

Genomics and pharmacogenomics of schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/20718829 [199]

"Schizophrenia (SCZ) is among the most disabling of mental disorders…SCZ has a heritability estimated at 60-90%. Genetic studies in SCZ have revealed the presence of chromosome anomalies, copy number variants, multiple single-nucleotide polymorphisms of susceptibility distributed across the human genome, aberrant single nucleotide polymorphisms (SNPs) in microRNA genes, mitochondrial DNA mutations, and epigenetic phenomena. Pharmacogenetic studies of psychotropic drug response have focused on determining the relationship between variation in specific candidate genes and the positive and adverse effects of drug treatment. Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and 95% of CYP3A4. About 10-20% of Western populations are defective in genes of the CYP superfamily. Only 26% of Southern Europeans are pure extensive metabolizers for the tri-genic cluster integrated by the CYP2D6+CYP2C19+CYP2C9 genes. The pharmacogenomic response of SCZ patients to conventional psychotropic drugs also depends on genetic variants associated with SCZ-related genes. Consequently, the incorporation of pharmacogenomic procedures both to drugs in development and drugs on the market would help to optimize therapeutics in SCZ and other central nervous system (CNS) disorders." [199]

Pharmacogenomics can improve antipsychotic treatment in schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/23606027 [200]

"Schizophrenia is a widespread mental disease with a prevalence of about 1% in the world population, and heritability of up to 80%. Drug therapy is an important approach to treating the disease. However, the curative effect of antipsychotic is far from satisfactory in terms of tolerability and side effects. Many studies have indicated that nearly 30% of patients exhibit little or no improvements associated with antipsychotics. The response of individual patients who are given the same dose of the same drug varies considerably. In addition, antipsychotic drugs are often accompanied by adverse drug reactions (ADRs), which can cause considerable financial loss in addition to the obvious societal harm. So, it is strongly recommended that personalized medicine should be implemented both to improve drug efficacy and to minimize adverse events and toxicity. There is therefore a need for pharmacogenomic studies into the factors affecting response of schizophrenia patients to antipsychotic drugs to provide informed

guidance for clinicians. Individual differences in drug response is due to a combination of many complex factors including ADEM (absorption, distribution, metabolism, excretion) process, transporting, binding with receptor and intracellular signal transduction. Pharmacogenetic and pharmacogenomic studies have successfully identified genetic variants that contribute to this interindividual variability in antipsychotics response. In addition, epigenetic factors such as methylation of DNA and regulation by miRNA have also been reported to play an important role in the complex interactions between the multiple genes and environmental factors which influence individual drug response phenotypes in patients. In this review, we will focus on the latest research on polymorphisms of candidate genes that code for drug metabolic enzymes (CYP2D6, CYP1A2, CYP3A4, etc.), drug transporters (mainly ABCB1) and neurotransmitter receptors (dopamine receptors and serotonin receptors, etc.). We also discuss the genome-wide pharmacogenomic study of schizophrenia and review the current state of knowledge on epigenetics and potential clinical applications." [200]

Pharmacogenomic testing for neuropsychiatric drugs: current status of drug labeling, guidelines for using genetic information, and test options.

http://www.ncbi.nlm.nih.gov/pubmed/24523097 [231]

"Advancements in pharmacogenomics have introduced an increasing number of opportunities to bring personalized medicine into clinical practice. Understanding how and when to use this technology to guide pharmacotherapy used to treat psychiatric and neurological (neuropsychiatric) conditions remains a challenge for many clinicians. Currently, guidelines exist to assist clinicians in the use of existing genetic information for drug selection and/or dosing for the tricyclic antidepressants, carbamazepine, and phenytoin. Additional language in the product labeling suggests that genetic information may also be useful for determining the starting and target doses, as well as drug interaction potential, for a number of other drugs. In this review, we outline the current status of pharmacogenomic testing for neuropsychiatric drugs as it pertains to information contained in drug labeling, consensus guidelines, and test panels, as well as considerations related to obtaining tests for patients." [231]

Role of cytochrome P450 genotype in the steps toward personalized drug therapy.

http://www.ncbi.nlm.nih.gov/pubmed/23226058 [232]

"Genetic polymorphism for cytochrome 450 (P450) enzymes leads to interindividual variability in the plasma concentrations of many drugs. In some cases, P450 genotype results in decreased enzyme activity and an increased risk for adverse drug effects. For example, individuals with the CYP2D6 loss-of-function genotype are at increased risk for ventricular arrhythmia if treated with usual does of thioridazine. In other cases, P450 genotype may influence the dose of a drug required to achieve a desired effect. This is the case with warfarin, with lower doses often necessary in carriers of a variant CYP2C9*2 or *3 allele to avoid supra-therapeutic anticoagulation. When a prodrug, such as clopidogrel or codeine, must undergo hepatic biotransformation to its active form, a loss-of-function P450 genotype leads to reduced concentrations of the active drug and decreased drug efficacy. In contrast, patients with multiple CYP2D6 gene copies are at risk for opioid-related toxicity if treated with usual doses of codeine-containing analgesics. At least 25 drugs contain information in their US Food and Drug Administration-approved labeling regarding P450 genotype. The CYP2C9, CYP2C19, and CYP2D6 genes are the P450 genes most often cited. To date, integration of P450 genetic information into clinical decision making is limited. However, some institutions are beginning to embrace routine P450 genotyping to assist in the treatment of their patients. Genotyping for P450 variants may carry less risk for discrimination compared with genotyping for disease-associated variants. As such, P450 genotyping is likely to lead the way in the clinical implementation of pharmacogenomics. This review discusses variability in the CYP2C9, CYP2C19, and CYP2D6 genes and the implications of this for drug efficacy and safety." [232]

Copy number variations' effect on drug response still overlooked.

http://www.ncbi.nlm.nih.gov/pubmed/25742449 [264]

Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions.

http://www.ncbi.nlm.nih.gov/pubmed/25987241 [203]

"We evaluated the cost-effectiveness of one-time pharmacogenomic testing for preventing adverse drug reactions (ADRs) over a patient's lifetime. We developed a Markov-based Monte Carlo microsimulation model to represent the ADR events in the lifetime of each patient. The base-case considered a 40-year-old patient. We measured health outcomes in life years (LYs) and quality-adjusted LYs (QALYs) and estimated costs using 2013 US$. In the base-case, one-time genetic testing had an incremental cost-effectiveness ratio (ICER) of $43,165 (95% confidence interval (CI) is ($42, 769, $43,561)) per additional LY and $53,680 per additional QALY (95% CI is ($53, 182, $54,179)), hence under the base-case one-time genetic testing is cost-effective. The ICER values were most sensitive to the average probability of death due to ADR, reduction in ADR rate due to genetic testing, mean ADR rate and cost of genetic testing." [203]

Pharmacokinetic Pharmacogenetic Prescribing Guidelines for Antidepressants: A Template for Psychiatric Precision Medicine.

http://www.ncbi.nlm.nih.gov/pubmed/27289413 [244]

"Antidepressants are commonly prescribed medications in the United States, and there is increasing interest in individualizing treatment selection for more than 20 US Food and Drug Administration-approved treatments for major depressive disorder. Providing greater precision to pharmacotherapeutic recommendations for individual patients beyond the large-scale clinical trials evidence base can potentially reduce adverse effect toxicity profiles and increase response rates and overall effectiveness. It is increasingly recognized that genetic variation may contribute to this differential risk to benefit ratio and thus provides a unique opportunity to develop pharmacogenetic guidelines for psychiatry. Key studies and concepts that review the rationale for cytochrome P450 2D6 (CYP2D6) and cytochrome P450 2C19 (CYP2C19) genetic testing can be delineated by serum levels, adverse events, and clinical outcome measures (e.g, antidepressant response). In this article, we report the evidence that contributed to the implementation of pharmacokinetic pharmacogenetic guidelines for antidepressants primarily metabolized by CYP2D6 and CYP2C19." [244]

Genotype and co-medication dependent CYP2D6 metabolic activity: effects on serum concentrations of aripiprazole, haloperidol, risperidone, paliperidone and zuclopenthixol.
http://www.ncbi.nlm.nih.gov/pubmed/26514968 [265]

"Overall, 6.1 % UM (n = 5), 25.6 % EM-f (n = 21), 46.3 % EM-s (n = 38), 1.2 % EM-s/EM-f (n = 1), 6.1 % IM (n = 5), and 14.6 % PM (n = 12) were found, taking co-administration of strong and moderate CYP2D6 inhibitors into account (pheno-conversion). It was demonstrated that CYP2D6 polymorphisms affect the serum concentrations of aripiprazole (n = 18), haloperidol (n = 11), risperidone (n = 20), and zuclopenthixol (n = 6), while no influence was seen on the paliperidone serum concentrations (n = 31)." [265]

Pharmacogenetics for Safe Codeine Use in Sickle Cell Disease.
http://www.ncbi.nlm.nih.gov/pubmed/27335380 [266]

"Here we describe the implementation of pharmacogenetics-based codeine prescribing that accounts for CYP2D6 metabolizer status. Clinical decision support was implemented within the electronic health record to guide prescribing of codeine with the goal of preventing its use after tonsillectomy or adenoidectomy and in CYP2D6 ultra-rapid and poor metabolizer (high-risk) genotypes. As of June 2015, CYP2D6 genotype results had been reported for 2468 unique patients. Of the 830 patients with sickle cell disease, 621 (75%) had a CYP2D6 genotype result; 7.1% were ultra-rapid or possible ultra-rapid metabolizers, and 1.4% were poor metabolizers. Interruptive alerts recommended against codeine for patients with high-risk CYP2D6 status. None of the patients with an ultra-rapid or poor metabolizer genotype were prescribed codeine. Using genetics to tailor analgesic prescribing retained an important therapeutic option by limiting codeine use to patients who could safely receive and benefit from it. Our efforts represent an evidence-based, innovative medication safety strategy to prevent adverse drug events, which is a model for the use of pharmacogenetics to optimize drug therapy in specialized pediatric populations." [266]

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 [72]

The Human Cytochrome P450 (CYP) Allele Nomenclature Database.
http://www.cypalleles.ki.se [178]

PharmGKB The Pharmacogenomics Knowledgebase.
https://www.pharmgkb.org/ [179]

Clinical applications of CYP genotyping in psychiatry.
http://www.ncbi.nlm.nih.gov/pubmed/25200585 [180]

Pharmacogenomics of drug-metabolizing enzymes: a recent update on clinical implications and endogenous effects.
http://www.ncbi.nlm.nih.gov/pubmed/23089672 [181]

Applications of CYP450 testing in the clinical setting.
http://www.ncbi.nlm.nih.gov/pubmed/23588782 [207]

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, 72, 178-181, 207]

Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver.
http://www.ncbi.nlm.nih.gov/pubmed/20538623 [182]

"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." [182]

CYP450 pharmacogenetic treatment strategies for antipsychotics: a review of the evidence.
http://www.ncbi.nlm.nih.gov/pubmed/23870808 [183]

"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." [183]

The Dosing of Atypical Antipsychotics.
http://www.ncbi.nlm.nih.gov/pubmed/15883149 [186]

"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." [186]

CYP3A5 Genetic Polymorphisms in Different Ethnic Populations.
http://www.ncbi.nlm.nih.gov/pubmed/15833928 [267]

"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." [267]

Lurasidone drug-drug interaction studies: a comprehensive review.
http://www.ncbi.nlm.nih.gov/pubmed/24825095 [268]

"Lurasidone PK is altered by strong cytochrome P450 (CYP) 3A4 inhibitors or inducers, and co-administration is contraindicated; whereas moderate CYP3A4 inhibitors have less effect, and lurasidone dosage restrictions are recommended." [268]

Genomics and pharmacogenomics of schizophrenia.
http://www.ncbi.nlm.nih.gov/pubmed/20718829 [199]

"Schizophrenia (SCZ) is among the most disabling of mental disorders…SCZ has a heritability estimated at 60-90%. Genetic studies in SCZ have revealed the presence of chromosome anomalies, copy number variants, multiple single-nucleotide polymorphisms of susceptibility distributed across the human genome, aberrant single nucleotide polymorphisms (SNPs) in microRNA genes, mitochondrial DNA mutations, and epigenetic phenomena. Pharmacogenetic studies of psychotropic drug response have focused on determining the relationship between variation in specific candidate genes and the positive and adverse effects of drug treatment. Approximately, 18% of neuroleptics are major substrates of CYP1A2 enzymes, 40% of CYP2D6, and 23% of CYP3A4; 24% of antidepressants are major substrates of CYP1A2 enzymes, 5% of CYP2B6, 38% of CYP2C19, 85% of CYP2D6, and 38% of CYP3A4; 7% of benzodiazepines are major substrates of CYP2C19 enzymes, 20% of CYP2D6, and 95% of CYP3A4. About 10-20% of Western populations are defective in genes of the CYP superfamily. Only 26% of Southern Europeans are pure extensive metabolizers for the tri-genic cluster integrated by the CYP2D6+CYP2C19+CYP2C9 genes. The pharmacogenomic response of SCZ patients to conventional psychotropic drugs also depends on genetic variants associated with SCZ-related genes. Consequently, the

incorporation of pharmacogenomic procedures both to drugs in development and drugs on the market would help to optimize therapeutics in SCZ and other central nervous system (CNS) disorders." [199]

Pharmacogenomics can improve antipsychotic treatment in schizophrenia.

http://www.ncbi.nlm.nih.gov/pubmed/23606027 [200]

"Schizophrenia is a widespread mental disease with a prevalence of about 1% in the world population, and heritability of up to 80%. Drug therapy is an important approach to treating the disease. However, the curative effect of antipsychotic is far from satisfactory in terms of tolerability and side effects. Many studies have indicated that nearly 30% of patients exhibit little or no improvements associated with antipsychotics. The response of individual patients who are given the same dose of the same drug varies considerably. In addition, antipsychotic drugs are often accompanied by adverse drug reactions (ADRs), which can cause considerable financial loss in addition to the obvious societal harm. So, it is strongly recommended that personalized medicine should be implemented both to improve drug efficacy and to minimize adverse events and toxicity. There is therefore a need for pharmacogenomic studies into the factors affecting response of schizophrenia patients to antipsychotic drugs to provide informed guidance for clinicians. Individual differences in drug response is due to a combination of many complex factors including ADEM (absorption, distribution, metabolism, excretion) process, transporting, binding with receptor and intracellular signal transduction. Pharmacogenetic and pharmacogenomic studies have successfully identified genetic variants that contribute to this interindividual variability in antipsychotics response. In addition, epigenetic factors such as methylation of DNA and regulation by miRNA have also been reported to play an important role in the complex interactions between the multiple genes and environmental factors which influence individual drug response phenotypes in patients. In this review, we will focus on the latest research on polymorphisms of candidate genes that code for drug metabolic enzymes (CYP2D6, CYP1A2, CYP3A4, etc.), drug transporters (mainly ABCB1) and neurotransmitter receptors (dopamine receptors and serotonin receptors, etc.). We also discuss the genome-wide pharmacogenomic study of schizophrenia and review the current state of knowledge on epigenetics and potential clinical applications." [200]

Pharmacogenomics study in a Taiwan methadone maintenance cohort.

http://www.ncbi.nlm.nih.gov/pubmed/25278738 [216]

"Pharmacogenomics is research to study the drug treatment responses in subgroups of patients according to their genetic variants or genetic expression information. Methadone maintenance treatment, which is usually prescribed for patients with heroin dependence, was launched in Taiwan by the government in 2006. In this study, 366 patients who had taken methadone continually in the previous 7 days were examined. Data from administration of the Treatment Outcomes Profile (TOP), Severity of Dependence Scale (SDS), Clinical Opioid Withdrawal Scale (COWS), and Treatment Emergent Symptoms Scale (TESS) were obtained from patients' report records. Genes encoding the liver cytochrome P-450 (CYP) enzymes that are involved with the metabolism of methadone (CYP2B6, 3A4 and 2C19) were selected and genotyped in this cohort. We found that the SNPs on CYP2B6 were associated with plasma S-methadone concentration; SNPs on CYP3A4 were associated with withdrawal symptoms and side effects; and SNPs on CYP2C19 were associated with methadone dose. SNPs in the genes encoding the morphine phase II metabolic enzyme, UGT2B7, were associated with withdrawal symptom scores. In pharmacodynamic genes, the SNPs on OPRM1 were associated with insomnia and change in libido side effects. We conclude that SNP markers may be useful for future methadone dosage adjustment and to reduce adverse reactions." [216]

The Absence of CYP3A5*3 Is a Protective Factor to Anticonvulsants Hypersensitivity Reactions: A Case-Control Study in Brazilian Subjects.

http://www.ncbi.nlm.nih.gov/pubmed/26291084 [269]

"Although aromatic anticonvulsants are usually well tolerated, they can cause cutaneous adverse drug reactions in up to 10% of patients. The clinical manifestations of the antiepileptic-induced hypersensitivity reactions (AHR) vary from mild skin rashes to severe cutaneous drug adverse reactions which are related to high mortality and significant morbidity. Genetic polymorphisms in cytochrome P450 genes are associated with altered enzymatic activity and may contribute to the risk of AHR. Here we present a case-control study in which we genotyped SNPs of CYP2C19, 2C9 and 3A5 of 55 individuals with varying severities of AHR, 83 tolerant, and 366 healthy control subjects from São Paulo, Brazil. Clinical characterization was based on standardized scoring systems and drug patch test. All in vivo investigation followed the ENDA (European Network of Drug Allergy) recommendations. Genotype was determined by real time PCR using peripheral blood DNA as a template. Of all 504 subjects, 65% were females, 45% self-identified as Afro-American, 38% as Caucasian and 17% as having non-African mixed ascendancy. Amongst 55 subjects with AHR, 44 had severe cutaneous drug adverse reactions. Of the 46 drug patch tests performed, 29 (63%) were positive. We found a strong association between the absence of CYP3A5*3 and tolerant subjects when compared to AHR ($p = 0.0002$, OR = 5.28 [CI95% 2.09-14.84]). None of our groups presented positive association with CYP2C19 and 2C9 polymorphisms, however, both SNPs contributed to separation of cases and tolerants in a Classification and Regression Tree. Our findings indicate that drug metabolism genes can contribute in the tolerability of antiepileptics. CYP3A5*3 is the most prevalent CYP3A5 allele associated with reduced enzymatic function. The current study provides evidence that normal CYP3A5 activity might be a protective factor to aromatic antiepileptics-induced hypersensitivity reactions in Brazilian subjects." [269]

Cost-effectiveness of one-time genetic testing to minimize lifetime adverse drug reactions.
http://www.ncbi.nlm.nih.gov/pubmed/25987241 [203]

"We evaluated the cost-effectiveness of one-time pharmacogenomic testing for preventing adverse drug reactions (ADRs) over a patient's lifetime. We developed a Markov-based Monte Carlo microsimulation model to represent the ADR events in the lifetime of each patient. The base-case considered a 40-year-old patient. We measured health outcomes in life years (LYs) and quality-adjusted LYs (QALYs) and estimated costs using 2013 US$. In the base-case, one-time genetic testing had an incremental cost-effectiveness ratio (ICER) of $43,165 (95% confidence interval (CI) is ($42, 769, $43,561)) per additional LY and $53,680 per additional QALY (95% CI is ($53, 182, $54,179)), hence under the base-case one-time genetic testing is cost-effective. The ICER values were most sensitive to the average probability of death due to ADR, reduction in ADR rate due to genetic testing, mean ADR rate and cost of genetic testing." [203]

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