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Serotonergic gene variation in substance use pharmacotherapy: a systematic review

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Abstract

Drug addiction is a serious disease with damaging effects on the brain and physical health. Despite the increase in the number of affected individuals, there are few effective pharmacological treatment options for substance use disorders. The study of the influence of an individual's genetic features on the treatment response may help to identify more efficacious treatment options. This systematic review focuses on the serotonergic system because of its relevant role in mood and impulse control disorders, and its contribution to the development and maintenance of drug use disorders. In particular, we examine the role of serotonergic genes in the response to pharmacotherapy for alcohol, cocaine and nicotine addiction. Current evidence suggests that genetic variability of the serotonergic biosynthesis enzyme tryptophan hydroxylase 2 (*TPH2*) and the serotonin transporter (*SLC6A4*) genes mediates the efficacy of several addiction treatments, such as ondansetron and disulfiram, and the antidepressants bupropion, nortriptyline and sertraline.

Keywords

addiction; bupropion; disulfiram; gene; ondansetron; serotonergic; sertraline; treatment

Background

Despite being a preventable disease, drug addiction is the leading cause of disability, illness and health-related economic burden in the USA [1]. For instance, it is estimated that over $122 billion per year is lost due to decreased productivity and addiction-related behavior [2]. The development of addiction disorders is primarily based on motivational factors. Alongside the habituation to increased drug intake, prolonged drug use may affect the individuals' ability to cope with cravings and lead to relapse following abstinence [3].

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Therefore, there is a need for efficacious treatments that break the cessation and relapse cycle, and inhibit impulsive drug-seeking behaviors.

The understanding of the neurochemical mechanisms implicated in drug use disorders is essential for the development of novel treatments for addiction. Abused drugs have a potent effect on the brain reward mechanisms and on neurotransmitter systems, such as serotonin (5-hydroxytryptamine; 5-HT), dopamine (DA) [4] and opioid [5]. Drugs, such as alcohol, nicotine and psychostimulants alter the activity of the 5-HT, DA [6] and opioidergic systems [7]. In particular, abnormally low 5-HT levels increase the risk for vulnerability to develop mood disorders and increase reward seeking behaviors, as well as contributing to the maintenance of addictive behaviors [8]. In this review, first we will describe the serotonergic system given the relevant role of serotonin within the brain reward network and, second, we will systematically search the literature for papers illustrating the role of variants of serotonergic receptor genes in the pharmacologic treatment of alcohol, cocaine and nicotine use disorders. In a previous review, we systematically examined the role of variation in the opioid system in the treatment of drug-use disorders [9].

Serotonergic system

Dysregulation of the serotonergic system has been found to be associated with mood disorders, suicidality, impulsivity and substance-related disorders [10]. The majority of the serotonergic neurons of the central nervous system originate in the raphe nucleus of the brain stem and project throughout the entire brain [14]. The precursor of serotonin, L-tryptophan, is obtained via dietary intake and is transported into the brain via the blood–brain barrier. The synthesis of serotonin occurs via the hydroxylation of L-tryptophan to 5-hydroxytryptophan (5-HTP) by the biosynthesis enzyme tryptophan hydroxylase. 5-HTP is subsequently decarboxylated to serotonin (5-HT) [11].

Tryptophan hydroxylase is the rate-limiting enzyme in the production of serotonin [12] and is encoded by the *TPH2* and *TPH1* genes. *TPH2* is localized to chromosome 12q21.1 and is the major isoform expressed in the brain [13]. Substance use disorders have been associated with a synonymous variant 1125A>T (rs4290270) in exon 9 of *TPH2* and an intron 7 variant of *TPH1* [14,15]. The *TPH2* variant 1125A>T (rs4290270) has been demonstrated to be a marker for allelic imbalance with the T allele being expressed at twice the level of the A allele [16]. As a result, individuals with a TT genotype may produce more serotonin than do A-allele carriers.

In the brain, 5-HT is released into the synaptic cleft following membrane depolarization where it binds to pre- and postsynaptic serotonergic receptors. Synaptic serotonin levels are regulated by reuptake by the serotonin transporter (5-HTT) that is located in the presynaptic terminal of serotonergic neurons [13]. 5-HTT is encoded by the *SLC6A4* gene that is situated on chromosome 17q11.2. There is a trial-lelic variable number tandem repeat polymorphism, *5-HTTLPR* [17] in the promoter region of this gene. Two common forms of this polymorphism are the long (L) version containing 16 repeats of 20–23 nucleotides and the short (S) version containing 14 repeats. The L allele has higher transcriptional activity than does the S allele [17]. An A–G transition (rs25531) is found within the L allele of the 5-

HTTLPR. The G form of the allele has lower transcriptional activity and its expression is similar to that of the S allele [18,19]. The two low-expressing alleles (L_G and S) are often referred to as S′, while the higher activity L_A allele is referred to as L′. If the rs25531 variation was not assessed, L is used for the L_A and L_G alleles. Another serotonin transporter variant, rs1042173, is located in in a putative microRNA binding and polyadenylation signal site in the 3' untranslated region (3_UTR) of the 5-HTT gene. Constructs with the rs10421731 G allele expressed higher mRNA and protein levels in cellular transfection assays than did T allele constructs [20].

Drug use disorders & the serotonergic system

The most investigated neurotransmitters associated with drug use disorders are the 5-HT and the DA systems. In particular, postsynaptic 5-HT_{1A} and 5-HT_{2A} receptors enhance mesocorticolimbic DA activity via their action on ventral tegmental area neurons [21]. Similarly, 5-HT_{1B} and 5-HT_{2C} postsynaptic receptors situated in the ventral tegmental area inhibit the release of GABA and lead to enhanced mesocorticolimbic DA release. Binding of 5-HT to the 5-HT_{2C} receptor increases synaptic DA levels further regulates DA exocytosis and DA neuronal firing [22] and is centrally involved in cocaine seeking behavior in rodents [23]. Drugs of abuse such as cocaine block the functioning of the 5-HT, DA and norepinephrine transporters, leading to increased levels of their respective neurotransmitters [24]. In addition, 5-HT_{2A} receptor antagonists blocks cocaine sensitization while 5-HT_{2A} agonists amplify the stimulant effects of cocaine [25]. In summary, 5-HT modulates DA release and plays a large role in the development of drug use disorders.

Literature search

Scopus (all databases) and PubMed were systematically searched with no language or year restrictions up to August 2014 for research articles addressing the relationship among gene polymorphism, pharmacogenetics, serotonin and response. Selected search terms were `serotonin,' `gene,' `polymorphism,' `substance abuse,' `treatment' and `response' occurring either anywhere in the article (for PubMed) or in the case of Scopus, in the title, abstract or keywords only. Inclusion was restricted to studies with clinical populations suffering from addictive disorders, such as substance use and dependence for drugs of abuse, that investigated gene polymorphisms, and reported specific measures of treatment response. Excluded studies were those using animal models, clinical populations with mood disorders and clinical trials with psychotropic drugs. All data were extracted by three nonblinded reviewers (IB, DG and DN) to determine if studies met inclusion criteria and, in cases where this information was not provided in the abstract, full text was obtained. All papers identified were published in English. Duplicates, review articles and articles not fulfilling the search criteria were removed (Figure 1). Table 1 summarizes the findings of the eight studies included in this systematic review. Figure 1.

Alcohol

Ondansetron

The 5-HT_3 receptor antagonist ondansetron is effective in inhibiting heavy drinking behaviors in those with early-onset alcoholism. The advantages of this treatment include mood enhancing and anticraving properties [26]. There is strong evidence that ondansetron-treated patients experience longer periods of abstinence and reduced alcohol consumption compared with individuals on a placebo treatment. Furthermore, *5-HTTLPR* L′L′ homozygous subjects respond better to ondansetron in terms of reduced alcohol consumption and increased abstinence duration than did those with at least one S′ allele [27]. In addition, the genetic variant rs1042173 in the 3'UTR of the 5-HTT gene has been linked to increased response to ondansetron. In particular, subjects with the *5-HTTLPR* L′L′ and the *rs1042173* TT 3′UTR genotype pattern treated with ondansetron consumed less alcohol and experienced extended abstinence periods compared with those without this genotype pattern.

A recent study investigated treatment response to ondansetron in relation to 18 common polymorphisms in the *5-HTR_{3A}* (HRT3A) and *5-HTR_{3B}* (HTR3B) genes [28]. The authors reported that patients carrying one or more of the genotypes rs1150226-AG or rs1176713-GG (in *HTR_{3A}*), rs17614942-AC (in *HTR_{3B}*) or rs1042173-TT (in *SLC6A4*) is predictive of a reduced number of daily drinks and enhanced abstinence in ondansetron-treated alcohol-dependent individuals. Seneviratne *et al*. compared the effects of an 11-week ondansetron treatment on the severity of drinking in those carrying the LL genotype compared with the LS/SS genotypes of the *5-HTT* gene [29]. Only in those with the *5-HTTLPR* L′L′ genotypes was drinking severity found to be associated positively with *5-HTT* mRNA levels in white blood cells. The decreased drinking severity found in ondansetron-treated L′L′ homozygotes may be linked to a decrease in *5-HTT* mRNA levels. The authors concluded that these two markers, 5-*HTTLPR* genotype and *5-HTT* mRNA levels, may assist in predicting treatment response to ondansetron.

Sertraline

Another treatment option for alcohol use disorders is sertraline, a selective serotonin reuptake inhibitor. One study has shown that late-onset *5-HTTLPR* L′L′ homozygous subjects responded better to sertraline than did S′-allele carriers [30]. A follow-up study on the same cohort [31] found that the beneficial effect of sertraline on alcohol consumption persisted for 3–6 months in the late-onset alcohol users with the L′L′ genotype, but was not maintained in the S′ carriers.

Kenna *et al*. investigated the effects of sertraline and ondansetron on alcohol use and found that untreated alcohol-dependent *5-HTTLPR* LL subjects drank less alcohol when treated with ondansetron or sertraline compared with individuals carrying a *5-HTTLPR* S allele [32]. By comparison, sertraline did not lead to beneficial effect in either group. Hence, treatment response to ondansetron and sertraline may be driven by the high-activity *5-HTTLPR* L allele.

Cocaine

Disulfiram

Disulfiram has been shown to be an effective treatment for alcohol disorders and cocaine addiction [33–38]. Clinical evidence indicates that this treatment reduces cocaine cravings [39,40], possibly by increasing DA levels and decreasing central and peripheral norepinephrine levels [41,42]. Disulfiram-treated cocaine addicts carrying the *TPH2* rs4290270 low-activity A allele have been shown to be better treatment responders than TT homozygous individuals [43]. This suggests that individuals who produce less serotonin exhibit a better response to disulfiram than those with a more efficient serotonergic metabolism. The same study showed that the *5-HTTLPR* S′-allele carriers had fewer cocaine-positive urines over the course of the interventional study than did L′L′ homozygous subjects [43]. This suggests that cocaine-dependent S′ carriers respond better to disulfiram [44–46] than L'L' subjects. Neuroimaging findings show that the S′ carriers of the *5-HTT* (*SLC6A4*) gene display abnormalities in functional activation in the amygdala in response to emotional stimuli [47]. Further S-carrier individuals have been shown to be at greater risk to develop depression and have more suicidal tendencies when exposed to stressful situations [17–19,48,49]. Thus, disulfiram appears to be more effective in S carriers, who may have increased vulnerability to emotional distress and substance abuse.

Nicotine

Quaak *et al*.'s study on the effects of the antidepressants bupropion and nortriptyline on smoking cessation found a strong relationship between three variants of the *5-HTT* gene *SLC6A4* (5-HTTLPR, STin2 and rs25531) and nicotine consumption [50]. Bupropion-treated individuals carrying the high-activity *5-HTTLPR* L′ allele displayed better long-term cessation rates than did placebo-treated subjects. Nortriptyline-improved abstinence rates but results were not statistically significant. The presence of the high-activity alleles L′ (for *5-HTTLPR*), STin2.12 (for STin2) and the A-rs25531 allele led to enhanced cessation and abstinence rates in response to bupropion and nortriptyline. The inhibition of tobacco cravings may be associated with the inhibitory action of bupropion and nortriptyline on mechanisms of action of the serotonin transporter and reuptake of serotonin. The authors argued that, although bupropion acts as a dopamine and norepinephrine reuptake inhibitor, its action on norepinephrine may lead to an increase in the firing rate of serotonergic neurons.

Conclusion

The serotonergic and dopaminergic systems play important roles in the development and maintenance of substance abuse and in relapse following abstinence. Within this context, this review illustrates how variants in the serotonergic biosynthetic enzyme tryptophan hydroxylase (*TPH2*) and the *5-HTT SLC6A4* genes moderate response to treatments for substance use disorders, such as disulfiram, ondansetron, sertraline and the a ntidepressants bupropion and nortriptyline.

It becomes apparent that there are a lack of studies that focus on the role of genetic variation in genes coding for the serotonergic receptors in addiction pharmacotherapy. Among the eight articles reviewed here (Table 1) the first three were from the same sample, the fifth and sixth articles were from another sample and the fourth was from a sample of only 15 subjects. This high degree of overlap, combined with a single article covering cocaine dependence and one on nicotine dependence shows that this research area is still in its infancy. Further, only one longitudinal study [31] has examined the association between treatment response and serotonergic genetic variants over time. Another methodological limitation of the studies reviewed here is related to the demographics of the populations. Most of the subjects were living in the USA and Europe, with a large majority in middle to early adulthood and being males. The frequencies of many polymorphisms vary by ethnicity making it essential to evaluate the majority of e thnicities found in the general population as well as to control population structure in the subsequent analyses.

In the last decade a number of initiatives have attempted to integrate pharmacogenomics data into the development of pharmacotherapies as well as in clinical practice [51]. For example, new guidelines have recently been developed to adjust the dosage of the antidepressant amitriptyline [52] and the antipsychotic aripiprazole [53] based on the presence of polymorphisms in the *CYP2D6* and *CYP2C19* genes. However, data cannot be easily translated into medical decision making given the inconsistencies in the literature and, as such, potential guidelines should be considered as optional.

In conclusion, addiction pharmacogenetics is a promising field and additional research is needed to identify genes and variants that predict the success of treatments, their clinical outcomes and potential side effects.

Future perspective

One could expect that inconsistencies in the literature will be addressed by providing specific scientific and ethical guidelines for the conduct of clinical trials in pharmacogenetics, by agreeing on levels of evidence that would define whether a finding can be used as a clinical decision-making tool, and by encouraging closer collaboration and communication among researchers and health professionals. Further, given that serotonergic gene variants mediate the efficacy of several addiction treatments, future studies should focus on investigating the physiological response associated with a wide range of polymorphisms to predict adverse side effects and treatment oucomes. Additionally, one can envisage that in the next 5 to 10 years clinical trials will start testing the effectiveness of i ndividualized drug addiction treatments.

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Executive summary

- Pharmacogenetics is a promising field that has the potential to improve patient care and reduce healthcare costs related to drug addiction.
- Genetic variability of the serotonergic biosynthesis enzyme tryptophan hydroxylase 2 (*TPH2*) and the serotonin transporter (*SLC6A4*) genes mediates the efficacy of several addiction treatments, such as ondansetron, disulfiram and the antidepressants bupropion, sertraline and nortriptyline.
- More research is needed to identify additional serotonergic gene variants that predict the success of treatments, their clinical outcomes and potential side effects of therapeutic interventions for drug addiction.

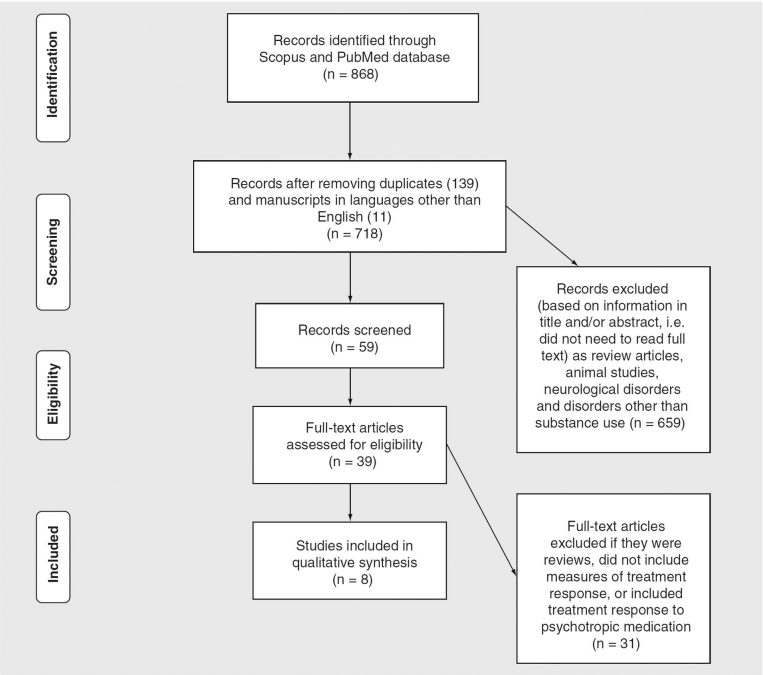

Figure 1.

PRISMA flowchart showing the filtering process used to select the eight studies included in the systematic review of studies investigating the relationship between variants of serotonergic receptors gene and treatment response in substance use pharmacotherapy.

Table 1

Description of the eight studies examining the relationship between serotonergic receptor genes and treatment response to pharmacotherapies of drug addiction.

Study	Sample (total n and age-M ± SD years)	Gender (% male)	Addiction	Design	End points	Results	Ref.
Ondansetron							
Johnson *et al*. 2013	n = 283 (45 ± 12)	73%	Alcohol	11 week, randomized, double-blind clinical trial with either ondansetron (4 μg/kg twice daily) or placebo, both with weekly cognitive behavioral therapy	Drinks per drinking day Percentage of heavy drinking days Percentage of days abstinent	Variants of *HTR3A* and *HTR3B* genes, along with the SLC6A4-LL/TT genotypes are associated with reduced drinking and higher abstinence rates in ondansetron-treated alcohol users	[28]
Seneviratne *et al*. 2012	n = 283 Ondansetron LL: 54.1 ± 8.8 LS/SS: 52.1 ± 16.6 Placebo: LL: 49.6 ± 14.5 LS/SS: 55 ± 13	Ondansetron: LL: 43% LS/SS: 75% Placebo: LL: 57% LS/SS: 93%	Alcohol	11 week, randomized, placebo-controlled, double-blind trial	Severity of drinking Relationship between 5-HTT mRNA white blood levels and *5′-HTTLPR* (measured at weeks 0,4,11) Self-reported consumption	In ondansentron-treated LL carriers decreased drinking severity was associated with a decrease in 5-HTTP mRNA levels	[29]
Johnson *et al*. 2011	n = 283 (45 ± 12.3)	73%	Alcohol	Ondansetron (4 μg/kg twice daily) or placebo combined with cognitive-behavioral therapy for 11 weeks	Number of drinks Length of abstinence	Lower number of drinks and higher abstinence rates in LL compared with LS/SS genotypes taking ondansetron	[27]
Kenna *et al*. 2009	n = 15 (44 ±9.5)	80%	Alcohol	Sertraline (200 mg/day) or ondansetron (0.5 mg/day) for 3 weeks, followed by an alcohol self-administration experiment (ASAE). Participants subsequently received placebo for 3 weeks, followed by a second ASAE	Drinking outcome	Ondansetron-improved drinking outcomes in LL subjects	[32]
Sertraline							
Kranzler *et al*. 2011	n = 134 (47.5 ± 1)	81%	Alcohol	Subjects assigned to either sertraline (200 mg/d) or placebo After 12 weeks of treatment, study medication was tapered over 2 weeks and discontinued During treatment, subjects received up to nine coping skills training sessions (i.e., sessions held weekly for 6 weeks, then biweekly for 6 weeks)	Drinking days Heavy drinking days	*5-HTTLPR* L'L' genotype subjects drank less alcohol when treated with sertraline compared with individuals carrying the S'allele	[30]

Study	Sample (total n and age-M ± SD years)	Gender (% male)	Addiction	Design	End points	Results	Ref.
Kranzler *et al.* 2012	n = 134 (47.5 ± 1)	80.6%	Alcohol	Same as in Kranzler *et al.* (2011)	Follow-up study of Kranzler *et al.* (2011)	At 3-month follow-up sertraline-treated L'/L' exhibited less drinking days than placebo with the same genotype	[31]
Disulfiram							
Nielsen *et al.* 2012	n = 71 Disulfiram S'S'/ L'S': 39 ± 9 L'L': 33 ± 14 Placebo S'S'/L'S':40 ± 11 L'L': 40 ± 12	Disulfiram S'S'/L'S': 67% L'L': 50% Placebo S'S'/L'S':63% L'L': 75%	Opioid and cocaine	Subjects on either disulfiram (250mg/day) or placebo	Positive urines	Subjects who were carriers of the *TPH2* low-activity A allele were better treatment responders than TT homozygous individuals Disulfiram-treated subjects with S'allele and *TPH2* A allele showed a reduction in urine cocaine levels from 71 to 53%	[43]
Bupropion and nortriptyline							
Quaak *et al.* 2012	n = 214 Placebo: 51.3 ± 9 Bupropion: 51.5 ± 8 Nortriptyline: 52 ± 9.3	Placebo: 63% Bupropion: 57% Nortriptyline: 71%	Nicotine	Subjects on either bupropion, nortriptyline and placebo	Abstinence from weeks 4–12, 4–26 and 4–52	*5-HTTLPR* L' carriers display prolonged cessation rates and abstinence rates with bupropion compared with S'S' genotype subjects	[50]