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Towards precision medicine in generalized anxiety disorder: Review of genetics and pharmaco(epi)genetics

Julia Tomasi[a,b], Amanda J. Lisoway[a,b], Clement C. Zai[a,b,c,d], Ricardo Harripaul[b,e], Daniel J. Müller[a,b,d], Gwyneth C.M. Zai[a,b,d,f], Randi E. McCabe[g,h], Margaret A. Richter[b,d,i], James L. Kennedy[a,b,d], Arun K. Tiwari[a,d,*]

[a] Molecular Brain Science Department, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada
[b] Institute of Medical Science, University of Toronto, Toronto, ON, Canada
[c] Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
[d] Department of Psychiatry, University of Toronto, Toronto, ON, Canada
[e] Molecular Neuropsychiatry & Development (MiND) Lab, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, ON, Canada
[f] General Adult Psychiatry and Health Systems Division, Centre for Addiction and Mental Health, Toronto, ON, Canada
[g] Department of Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada
[h] Anxiety Treatment and Research Clinic, St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada
[i] Frederick W. Thompson Anxiety Disorders Centre, Department of Psychiatry, Sunnybrook Health Sciences Centre, Toronto, ON, Canada

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ABSTRACT

Generalized anxiety disorder (GAD) is a prevalent and chronic mental disorder that elicits widespread functional impairment. Given the high degree of non-response/partial response among patients with GAD to available pharmacological treatments, there is a strong need for novel approaches that can optimize outcomes, and lead to medications that are safer and more effective. Although investigations have identified interesting targets predicting treatment response through pharmacogenetics (PGx), pharmaco-epigenetics, and neuroimaging methods, these studies are often solitary, not replicated, and carry several limitations. This review provides an overview of the current status of GAD genetics and PGx and presents potential strategies to improve treatment response by combining better phenotyping with PGx and improved analytical methods. These strategies carry the dual benefit of delivering data on biomarkers of treatment response as well as pointing to disease mechanisms through the biology of the markers associated with response. Overall, these efforts can serve to identify clinical, genetic, and epigenetic factors that can be incorporated into a pharmaco(epi)genetic test that may ultimately improve treatment response and reduce the socioeconomic burden of GAD.

1. Introduction

A recent report from the Global Burden of Disease estimated that one in six people worldwide have at least one mental or substance use disorder (Global Burden of Disease Collaborative Network, 2017; Ritchie and Roser, 2019). Anxiety disorders overall are the most common group of mental disorders, with the global current prevalence being 7.3% (Baxter et al., 2013). Approximately 11.6% of individuals worldwide are diagnosed with an anxiety disorder in a given year, with lifetime prevalence rates reaching as high as 31% in the United States (Baxter et al., 2013; Katzman et al., 2014). Unlike many other mental illnesses, anxiety disorders affect people earlier in life, reducing the number of years of being most productive (Craske et al., 2017). Generalized anxiety disorder (GAD) has been referred to as the "basic anxiety disorder" given that generalized anxiety is a component seen across other anxiety disorders (Brown et al., 2001). GAD is a chronic disorder characterized by marked anxiety and worry, occurring most days than not, for at least a period of six months. According to the DSM-5 criteria, the sufferer is unable to control the worry and these symptoms cause significant distress and impairment in important areas of functioning (American Psychiatric Association, 2013). Anxiety and worry are associated with three (or more) of the following six symptoms: (1) Restlessness, feeling keyed up or on edge; (2) Being easily fatigued; (3) Difficulty concentrating or mind going blank; (4) Irritability; (5) Muscle tension; and (6) Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep). GAD has a 12-month

* Corresponding author. Molecular Brain Science Department, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, 250 College Street, Toronto, Ontario, M5T 1R8, Canada.
E-mail address: arun.tiwari@camh.ca (A.K. Tiwari).

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prevalence of 2.9% and a lifetime prevalence of 6.2% (Kessler et al., 2012). GAD is more common in primary care settings where almost 7–8% of the patients report symptoms of excessive worrying that impairs their ability in school, at work, or in caring for their family (Kroenke et al., 2007). GAD and anxiety disorders in general tend to co-occur with and precede major depressive disorder (MDD), and have a high rate of comorbid substance use disorder, especially alcohol (Stein and Sareen, 2015). GAD is reported to be more prevalent among women, individuals of low socioeconomic status, those with a family history of GAD, and those reporting stressful life events in childhood (Moreno-Peral et al., 2014). Individuals with GAD are at a significantly higher risk of suicidal ideation and attempted suicides, compared to individuals without anxiety disorders (Cougle et al., 2009; Kanwar et al., 2013). Heritability estimates for GAD vary between 30 and 40% suggesting that both genetic and epigenetic factors are important contributors (Hettema et al., 2005).

Treatment of GAD initially includes lifestyle modification and/or low-intensity psychological intervention (e.g., self-help books, websites). Patients who fail to respond can receive more intensive psychological therapy (e.g., cognitive behavioural therapy (CBT)), pharmacotherapy, or a combination of the two (Stein and Sareen, 2015). Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) continue to be used extensively for treating GAD (Katzman et al., 2014; Stein and Sareen, 2015). Additional pharmacological treatment includes the use of benzodiazepines, buspirone, pregabalin, and antipsychotics. To prevent relapse of GAD, it has been suggested that pharmacotherapy should be continued for a minimum of six months to a year (Mochcovitch et al., 2017). Although antidepressants are the cornerstone of pharmacological treatment for anxiety disorders, only 50–60% of patients respond, and only 30–50% of patients reach remission (Reinhold and Rickels, 2015; Stein and Sareen, 2015). Non-responders have been shown to have worse treatment adherence, higher risk of relapse, greater risk of other psychiatric and non-psychiatric illnesses, and almost double the health care utilization compared to treatment responders (Al-Harbi, 2012). Thus, there is a very strong need for improvements in treatment for anxiety disorders in general. Towards this goal, investigations of factors influencing symptomatology and treatment response may identify targets that can be pursued to predict treatment outcomes, which can ultimately lead to the personalization of treatments and greater improvements for patients.

1.1. Genetic studies of GAD

Several genetic studies have used both hypothesis-based (candidate gene) as well as hypothesis-free (genome-wide association study, GWAS) methods to identify genes associated with susceptibility to anxiety disorders with little success. The main emphasis of candidate gene studies has been on stress-related pathways and monoaminergic system genes. For example, the short allele of the serotonin transporter-linked polymorphic region (5-HTTLPR) in the serotonin transporter gene (*SLC6A4*) has been associated with GAD (Chang et al., 2017; You et al., 2005). Other genes that have been implicated in GAD development include the genes for monoamine oxidase A (*MAOA*), serotonin receptor 1A (*HTR1A*), brain-derived neurotrophic factor (*BDNF*), neuropeptide Y (*NPY*), regulator of G protein signaling 2 (*RGS2*), proteasome modulator 9 (*PSMD9*), and adrenergic receptors alpha 1A and beta 2 (*ADRA1A*, *ADRB2*) (Amstadter et al., 2010; Gragnoli, 2014; Koenen et al., 2009; Molina et al., 2011; Moreira et al., 2015; Tadic et al., 2003; Zhang et al., 2017). Although these markers provide interesting targets to pursue further, all major psychiatric disorders are considered to be polygenic, and candidate gene studies are often underpowered (Duncan et al., 2019). Moreover, recent studies that have used large sample sizes to investigate whether historical candidate genes remain associated with MDD and schizophrenia have failed to show support for the candidate gene hypothesis (Border et al., 2019; Johnson et al., 2017). Also, given that many of the classic candidate genes from MDD and schizophrenia have not replicated in GWASs of these disorders, it is likely that candidate genes related to GAD, and anxiety disorders in general, will have a similar fate (Duncan et al., 2019). The narrow scope of analysis that candidate gene studies provide is remedied by GWASs. In a GWAS of GAD symptoms in patients of Hispanic and Latin American ancestry (n = 12,282), rs78602344 in the thrombospondin 2 (*THBS2*) gene was identified to be nominally associated with anxiety symptoms although this was not replicated in a subsequent meta-analysis (Dunn et al., 2017). A recent meta-analysis in over 18,000 unrelated individuals of European ancestry identified an intronic polymorphism, rs1709393, in an uncharacterized non-coding RNA locus (*LOC152225*) to be associated with a lifetime diagnosis of GAD, panic disorder, agoraphobia, social phobia, or specific phobia in a case-control analysis and rs1067327 within *CAMKMT* encoding the calmodulin-lysine N-methyltransferase gene in a quantitative phenotypic factor score analysis (Otowa et al., 2016). However, a challenge that remains in these studies is the need for larger sample sizes that will provide greater power to detect smaller effect sizes (Visscher et al., 2017). More recently, five genome-wide significant associations were identified in individuals of European ancestry from the UK Biobank who self-reported a lifetime professional diagnosis of an anxiety disorder (GAD, social phobia, panic disorder, agoraphobia, or specific phobia) or had likely DSM-IV GAD (cases = 25,435; controls = 58,113; Purves et al., 2019). The five loci are: an intergenic single nucleotide polymorphism (SNP) rs10809485 at 9p23, an intronic SNP rs1187280 in neurotrophic receptor tyrosine kinase 2 (*NTRK2*), a SNP rs3807866 upstream of transmembrane protein 106B (*TMEM106B*), an intergenic SNP rs2861139 on chromosome 5, and an intronic SNP rs4855559 in the myosin heavy chain 15 (*MYH15*) gene. A SNP from the 9p23 region (rs10959883) was replicated in the UK Biobank Neuroticism sample (n = 241,883) and the MDD sample from the Psychiatric Genomics Consortium (cases = 45,591; controls = 97,674) and rs3807866 in the neuroticism sample (Purves et al., 2019; Wray et al., 2018). This study further supports the observation that larger sample sizes, even with minimal phenotyping, can be used to identify disease-associated genetic variations.

1.2. Neuroimaging studies of GAD

Neuroimaging studies have identified brain region activation abnormalities and synchronization defects in patients with anxiety disorders, which can aid the establishment of biomarkers that can be targeted for treatment. The regional activation alterations that are consistently mentioned across anxiety disorders are a hyperactive amygdala in response to environmental threats and deficits in prefrontal attenuation of fear responses induced by the amygdala (Taylor and Whalen, 2015). In line with this, GAD is associated with increased amygdala grey matter volume and an increased activation of the amygdala that correlates with anxiety severity (Etkin et al., 2009; Monk et al., 2008). GAD is also associated with a decreased volume of white matter in the dorsolateral prefrontal cortex (dlPFC), anterior limb of the internal capsule (ALIC), and midbrain. This decreased dlPFC volume is correlated with greater symptom severity and duration of illness, and decreased ALIC volume is associated with increased symptom severity (Moon and Jeong, 2015).

The processing of facial affect is dysfunctional in GAD, reflecting a propensity to detect threat in the environment in an inflexible manner. Adolescents with GAD display greater ventrolateral PFC activations to angry faces than healthy adolescents, with this activation being correlated with decreased anxiety severity, which suggests the activation occurs for compensation purposes (Monk et al., 2006). GAD is associated with reduced connectivity of the amygdala with the ventral anterior cingulate cortex (vACC) and the ventromedial prefrontal cortex

(vmPFC), along with a hyperactive amygdala, while observing a face-word emotional conflict, suggesting that the lack of inhibitory action from the vACC and vmPFC may play a role in the deficits in fear inhibition and adaptation that exist among patients with GAD (Etkin et al., 2010). On the other hand, there is increased connectivity between the amygdala and dorsal ACC (dACC) and dorsal medial PFC (dmPFC) during emotional reactivity, which implies a role for the dACC and dmPFC in fear initiation and expression that appear to be excessive in GAD (Robinson et al., 2014).

Patients with GAD also demonstrate deficits in emotion regulation and associative learning. Emotion regulation abnormalities in GAD are reflected through deficient activity in the dlPFC, dmPFC, and dACC that occur during attempts at cognitive reappraisal of aversive photographs (Ball et al., 2013; Blair et al., 2012). GAD is also associated with a diminished ability of the vmPFC to differentiate fear-conditioned stimuli from stimuli that have similar characteristics, which demonstrates that deficits in associative learning and threat generalization processes in GAD may contribute to the disorder's origin (Greenberg et al., 2013).

Effective treatments for GAD have been shown to correct neuroimaging-identified abnormalities (Hoehn-Saric et al., 2004). The degree of treatment response has also been predicted through neuroimaging methodologies. Greater treatment response to venlafaxine in patients with GAD has been predicted by elevated pre-treatment reactivity in the rostral ACC and decreased reactivity in the amygdala to fearful faces, as well as increased pre-treatment ACC reactivity when anticipating aversive and neutral images (Nitschke et al., 2009; Whalen et al., 2008). Among youths with GAD, greater pre-treatment left amygdala activation while attending to their own internal responses to emotional cues was predictive of a higher response to fluoxetine or CBT (McClure et al., 2007). Thus, neuroimaging studies offer important clues towards understanding treatment response. Implementing routine neuroimaging in a clinical setting, especially primary care where most patients with anxiety disorders receive initial treatment, is a major challenge because of healthcare costs and accessibility. Until then, measures that can reliably estimate facial affect processing, emotion regulation, and associative learning may help in understanding and improving treatment response.

1.3. Pharmacogenetic studies of antidepressant response

There are only a limited number of studies that have investigated the pharmacogenetics (PGx) of response to pharmacotherapy in patients with GAD. Similar to antidepressant response studies in depression, the majority of studies have focused on genes from the serotonergic system. In particular, the 44 base pair insertion (long, L)/deletion (short, S) polymorphism (5-HTTLPR) in the promoter region of the serotonin transporter gene (*SLC6A4*, *5-HTT*) has been investigated. The short allele and the long allele carrying the G-variant of rs25531 (A > G) have been associated with reduced transcriptional activity (Hu et al., 2006). The results of the PGx studies for 5-HTTLPR have been mixed with one study reporting association of the S-allele carriers with reduced response to venlafaxine (Lohoff et al., 2013b), and another reporting no association in older adults with GAD (Lenze et al., 2010). Similarly, polymorphisms in serotonin receptor genes (*HTR1A, 1B, 2A, 2B*), catechol-O-methyltransferase (*COMT*), *BDNF*, dopamine D2 receptor (*DRD2*), dopamine transporter (*DAT1*), pituitary adenylate cyclase-activating polypeptide (*PACAP*), pituitary adenylate cyclase-activating polypeptide type 1 receptor (*PAC1*), neuropeptide S receptor 1 (*NPSR1*), and μ-opioid receptor (*OPRM1*) have been investigated with, at best, marginal associations (see Table 1) (Cooper et al., 2013a, 2013b; Gottschalk and Domschke, 2017; He et al., 2018; Lenze et al., 2013; Lin et al., 2018; Lohoff et al., 2013a; Narasimhan et al., 2011, 2012; Saung et al., 2014). In a large candidate gene study in GAD (61 genes, 825 polymorphisms, 259 subjects) using set based association testing, Perlis and colleagues identified 12 sets of SNPs in the corticotropin-releasing hormone receptor 1 (*CRHR1*, 3 SNPs), the dopamine receptor D3 (*DRD3*, 5 SNPs), glucocorticoid receptor (*NR3C1*, 3 SNPs), and phosphodiesterase 1A (*PDE1A*, 1 SNP) to be associated with duloxetine response (Perlis et al., 2013). More recently, a GWAS in 98 patients with GAD treated with venlafaxine XR (266,820 SNPs) failed to detect any genome-wide significant associations with response/remission (Jung et al., 2017).

The cytochrome P450 (CYP450) enzymes are primarily responsible for the metabolism of anxiolytic, antidepressant, and antipsychotic medications (Eichelbaum et al., 2006; Ingelman-Sundberg et al., 2007; Tiwari et al., 2009). Of particular interest are the CYP450 genes *CYP2D6* and *CYP2C19*, as there are several functional variants within these genes that can classify individuals as poor, intermediate, extensive, or ultra-rapid metabolizers (Bousman et al., 2019a; Tiwari et al., 2009). This information can be used to optimize drug dosage, reduce adverse effects, and guide medication selection. While studies on pharmacokinetic genes in GAD are lacking, it is reasonable to assume that these genes may influence antidepressant treatment response and side effects in individuals with GAD.

While PGx testing has the potential to improve antidepressant treatment outcomes, more research must be done to determine whether such testing produces clinically meaningful outcomes in terms of efficacy. Towards this goal, the large (n = 1167), randomized, blinded, and controlled GUIDED trial by Greden and colleagues investigated the utility of PGx testing to decide on medications for patients with MDD that have not achieved an adequate response to at least one antidepressant (Greden et al., 2019). There was no significant difference in symptom improvement for those that received PGx testing compared to the patients that received treatment-as-usual (TAU) (27.2% vs. 24.4%, p = 0.107). However, the secondary outcomes of improvements in response (26.0% vs. 19.9%, p = 0.013) and remission rates (15.3% vs. 10.1%, p = 0.007) did reach statistical significance. This study provides evidence that PGx testing may have promise for improving efficacy in patients with difficult-to-treat MDD. However, it has been criticized for having only modest clinical significance, number needed to treat values that are considered excessive, possible expectancy biases that could have occurred during the study, and a lack of stratification for variation in the prescribers' understanding of psychopharmacology (Goldberg et al., 2019). Although these concerns are valid, recent meta-analyses including several randomized controlled trials (RCTs) have shown that patients with MDD that received antidepressants using guidance from PGx testing are more likely to achieve remission from their symptoms than TAU (Bousman et al., 2019b; Rosenblat et al., 2018). Specifically, the meta-analysis investigating five RCTs comparing PGx-guided treatment with TAU showed that patients with MDD that received PGx-guided treatment were 1.71 times more likely to reach remission than TAU (p = 0.005) (Bousman et al., 2019b). The meta-analysis by Rosenblat and colleagues including four RCTs and two open-label, controlled cohort studies also supported the utility of PGx-guided treatment, showing pooled risk ratios for treatment response of 1.36 (p = 0.0006) and 1.74 for remission (p = 0.02), both in favour of PGx guidance rather than TAU (Rosenblat et al., 2018). Therefore, while trials assessing the efficacy of PGx testing carry important limitations and must be interpreted with caution, the evidence appears to suggest that PGx testing can be a viable tool to support medication decisions for those with treatment-resistant MDD. In regard to the efficacy of PGx-guided treatment for patients with anxiety disorders, only one study has been performed. This randomized, subject- and rater-blinded study by Bradley and colleagues compared PGx-guided treatment to TAU in patients with depression and/or anxiety (Bradley et al., 2018). Patients diagnosed with anxiety that had PGx-guided treatment had higher treatment response rates than those receiving TAU (OR: 1.76; p = 0.04) (Bradley et al., 2018). This study thus provides preliminary evidence of the utility of PGx testing among patients with anxiety disorders.

Table 1
Summary of pharmacogenetic studies of antidepressant response in GAD.

Gene(s) (SNP)	Sample Size[a]	Ethnicity	Drug Tested	Results	Study
SLC6A4 (5-HTTLPR/rs25531) *HTR2A* (rs7997012)	112	European American	Venlafaxine XR	Carriers of La/La + G/G or La/La + G/A had better treatment response than those with La/S + A/A or S/S + A/A to 6 months of venlafaxine XR ($p < 0.0001$)	Lohoff et al., 2013b
SLC6A4 (5-HTTLPR/rs25531)	125	European American	Escitalopram	Response to escitalopram not different between genotypes	Lenze et al., 2010
SLC6A4 (5-HTTLPR/rs25531), *HTR1A* (rs6295), *HTR1B* (rs11568817, rs130058, rs6296), *HTR2A* (rs6311)	133	Caucasian, African American	Escitalopram	Carriers of rs11568817 G allele from *HTR1B* and rs6311 A allele from *HTR2A* had greater declines in attention with 12-weeks of escitalopram compared to placebo (corrected $p < 0.008$)	Lenze et al., 2013
HTR2A (rs7997012)	112	European American	Venlafaxine XR	Higher response in G-allele carriers versus A/A genotype at 6-months of venlafaxine XR ($p = 0.008$)	Lohoff et al., 2013a
COMT (rs4680)	112	European American	Venlafaxine XR	Nominally significant association between A-allele (Met) and response after 6 months of venlafaxine XR measured by CGI-I ($p = 0.049$), but not by HAM-A	Narasimhan et al., 2012
BDNF (rs6265)	111	European American	Venlafaxine XR	No significant association between rs6265 and venlafaxine XR response	Narasimhan et al., 2011
BDNF (rs6265)	206 GAD, 209 healthy controls	Chinese Han	Escitalopram or Venlafaxine XR	No significant association between rs6265 and response to 8-weeks of escitalopram or venlafaxine XR	Lin et al., 2018
DRD2 (rs1076560, rs1800497) *DAT1* (rs2550948, VNTR)	156	European American, African American, other	Venlafaxine XR	None of the variants showed association with treatment response to 6 months of venlafaxine XR	Saung et al., 2014
PACAP (rs2856966, rs928978, rs1610037, rs1893154, rs2231187, rs2846811, rs8192595) *PAC1* (rs2267735)	109	European American	Venlafaxine XR	A-allele of rs2856966 was associated with better treatment response to 6-months of venlafaxine XR (corrected $p = 0.006$)	Cooper et al., 2013a
NPSR1 (rs324981)	137 GAD, 177 healthy controls	Chinese Han	Venlafaxine XR or Escitalopram	AA and TT carriers treated with venlafaxine XR had greater response compared to AT carriers ($p = 0.004$), while no response differences in patients on escitalopram	He et al., 2018
OPRM1 (rs1799971)	108	European American	Venlafaxine XR	No association between rs1799971 and response to 6-months of venlafaxine XR	Cooper et al., 2013b
825 SNPs in 61 candidate genes	259	Caucasian	Duloxetine	12 SNPs associated with duloxetine response in gene set-based association analysis: *CRHR1* (rs4792888, rs12942254, rs242925, $p < 0.01$), *DRD3* (rs963468, rs1486009, rs324026, rs324023, rs167770, $p < 0.01$), *NR3C1* (rs258747, rs6196, rs6198, $p = 0.053$), *PDE1A* (rs1549870, $p = 0.014$)	Perlis et al., 2013
GWAS (266,820 SNPs)	98	European American	Venlafaxine XR	No SNP reached genome-wide significance, but 8 SNPs marginally associated with treatment response/remission to venlafaxine XR at months 3 and 6 ($p < 0.00001$): rs10483832 (*MED6*), rs13216187 (*SGK1*), rs17154827, rs1993919 (*STAB2*), rs2136474 (*SPATA3*), rs7060140 (*OPHN1*), rs7342064 and rs7897283 (*PARD3*)	Jung et al., 2017

[a] The subjects for the studies were derived from randomized controlled trials.

1.4. Pharmaco-epigenetic studies of treatment response

Epigenetics refers to an area of research that studies chemical modification of the surface of the DNA which regulates gene activity, without altering the DNA sequence. Although many epigenetic processes have been identified in recent years, DNA methylation of CpG dinucleotides remains the most well-known and extensively studied epigenetic modification (Smith and Meissner, 2013). DNA methylation has been investigated in a number of stress-related psychiatric disorders, including MDD (Frieling and Tadic, 2013; Klengel et al., 2014; Menke et al., 2012; Schroeder et al., 2012). Furthermore, MDD, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), anxiety disorders, and schizophrenia have all been shown to involve epigenetic mechanisms to some degree (Daskalakis et al., 2018; Grunblatt et al., 2018; Klengel et al., 2014; Matosin et al., 2017; Mill and Petronis, 2007; Mill et al., 2008; Pal et al., 2016). Recently, a meta-analysis examining post-mortem prefrontal cortex (PFC) samples across psychiatric and neurodegenerative disorders revealed that co-expression and co-methylation signatures were enriched for biological processes within the stress response system (Zhu et al., 2019). This provides additional evidence that the stress response system, which is also dysregulated in anxiety disorders, may play a role in multiple neuropsychiatric disorders.

Pharmaco-epigenetics is a newly emerging area of research focused on the epigenetic alternations induced by a medication, associated with therapeutic response, or associated with medication side-effects. While pharmaco-epigenetic research is prevalent concerning antidepressant response in MDD, epigenetic research focusing on treatment response in anxiety disorders is currently very limited, and most studies focus on CBT. Specific to anxiety disorders, an epigenetic study by Roberts et al. revealed that response to CBT in children was associated with increased *SLC6A4* methylation levels at CpG site 4 (Roberts et al., 2014). In a subsequent study, Roberts et al. found that CBT response in children with anxiety was nominally associated with DNA methylation of the *FKBP5* gene, a glucocorticoid receptor co-chaperone gene involved in the stress response system (Roberts et al., 2015). More recently, the same research group examined DNA methylation across the *FKBP5* promoter region and intron 7 in 111 adult patients with agoraphobia. They found a decrease in DNA methylation at one CpG site within intron 7 to be associated with greater response to exposure-based CBT (Roberts et al., 2019). In adult patients with panic disorder, response to CBT was associated with increased methylation of the *MAOA* gene, reaching levels that were comparable to healthy controls, while a lack of response was associated with decreased methylation (Ziegler et al., 2016). Similarly, *MAOA* methylation was increased following 2 weeks of exposure therapy in females with acrophobia (fear of heights), and the increased methylation levels were correlated with decreasing symptoms (Schiele et al., 2018).

Considering that antidepressant pharmacotherapy is also an important treatment for anxiety disorders, we examined the state of pharmaco-epigenetic research for MDD in addition to anxiety (see Lisoway et al., 2018 for review). While these studies are not focused on patients with primary anxiety disorders, they examine the same antidepressant medications that are used in the treatment for anxiety disorders. The majority of antidepressant medications target the serotonin system and DNA methylation of the serotonin transporter gene (*SLC6A4*) has been investigated, but results are not well-replicated at this stage. Studies of *SLC6A4* methylation conducted by Domschke et al. and Kang et al. reported contrasting association findings of methylation levels with antidepressant response in MDD (Domschke et al., 2014; Kang et al., 2013). Domschke et al. found that decreased methylation was associated with impaired treatment response, while Kang et al. found a trend toward increased methylation associated with impaired response. Okada et al. also examined DNA methylation of the promoter region of *SLC6A4* in patients with MDD following antidepressant treatment, and found that the methylation rate of CpG site 3 was higher in responders compared to those that were poorer responders (Okada et al., 2014). The serotonin receptor 1A and 1B genes have also been investigated in studies of response to antidepressant treatment. Promoter region methylation of *HTR1B* was found to be negatively correlated with clinical improvement in children and adolescents treated with fluoxetine (Gasso et al., 2017). In addition, decreased *HTR1A* and *HTR1B* methylation was associated with impaired response to eight weeks of escitalopram treatment and interacted with high levels of life stress (Wang et al., 2018a). Finally, further research by Domschke et al. found no major influence of DNA methylation within the *MAOA* gene, which encodes the main enzyme responsible for degradation of serotonin, on antidepressant treatment response (Domschke et al., 2015). Overall, the serotonin system results are varied, making interpretation and generalizability difficult.

Other loci have also been investigated in the context of antidepressant response and DNA methylation in MDD. Lower levels of DNA methylation at CpG unit 5 of the interleukin 11 gene (*IL11)* have been associated with better antidepressant response, while higher DNA methylation levels at CpG unit 4 of *IL11* was associated with better response to escitalopram and worse response to nortriptyline (Powell et al., 2013). As well, decreased DNA methylation of the *BDNF* gene promoter region was associated with a lack of antidepressant treatment response (Tadic et al., 2014). However, in a group of patients with acute coronary syndrome and comorbid depression, increased pre-treatment methylation in the exon IV promoter of *BDNF* was associated with improvement in depressive symptoms following treatment with escitalopram (Kim et al., 2015). Furthermore, *BDNF* hypermethylation of four CpG sites predicted improved response to eight weeks of escitalopram treatment and average *BDNF* methylation levels increased in remitters following antidepressant treatment (Wang et al., 2018b). These researchers also found that increased *BDNF* methylation levels combined with lower life stress scores predict escitalopram response, providing additional evidence that stress levels may be an important clinical biomarker to consider when investigating treatment response in depressive disorders (Wang et al., 2018b).

Although the current state of pharmaco-epigenomic research has provided interesting findings and targets to explore further, majority of these studies are limited by their small sample sizes, failure to consider the effects of specific antidepressant medications, and heterogeneity of symptoms among patient samples. It is thus paramount that future studies take these limitations into account to establish more convincing evidence for epigenetic predictors of treatment response, especially among patients with anxiety disorders.

2. Towards the advancement of medication treatment response research in GAD

Current (epi)genetic, pharmaco(epi)genetic, and neuroimaging research efforts on GAD have identified interesting targets that warrant further investigation. However, there is an overall paucity of biomarker investigations for GAD, with the research being quite stagnant despite the significant need to improve treatments available for these patients. Alternative approaches are therefore needed in order to advance GAD research. Such approaches include the use of anxiety-related endophenotypes to study the (epi)genetics and pharmaco(epi)genetics of GAD, incorporating genetics into neuroimaging-related methodologies, applying rodent epigenetic findings to humans, and exploring strategies such as the use of genome-wide polygenic risk scores to identify treatment responders. Through the adoption of these strategies, which will be outlined in the following sections, GAD research may evolve to uncover factors that can be used to predict treatment response for patients, and as an extension, provide insight on the etiology of the disorder.

Table 2
Measures currently used to estimate anxiety endophenotypes.

Endophenotypes	Measures	Studies
Exaggerated startle reactivity	Eyeblink startle reflex (Electromyography)	Bakker et al., 2009; Gorka et al., 2017; Grillon et al., 2017; Lissek et al., 2014; Vaidyanathan et al., 2014; Waters et al., 2008
Carbon dioxide hypersensitivity	Carbon dioxide challenge	Battaglia et al., 2007; Caldirola et al., 1997; Telch et al., 2012
Anxiety sensitivity	Anxiety Sensitivity Index	National Institute of Mental Health
Behavioural inhibition	Behavioral Inhibition System scale	Clauss and Blackford, 2012; Frenkel et al., 2015; Maack et al., 2012; Paulus et al., 2015; Smith et al., 2012
Intolerance of uncertainty	Intolerance of Uncertainty scale	National Institute of Mental Health
Neuroticism	Eysenck Personality Questionnaire Neuroticism-Extraversion-Openness Personality Inventory	Andreescu et al., 2015; Okbay et al., 2016
Extreme response style	Neuroticism-Extraversion-Openness Personality Inventory Temperament Character Inventory Affective Neuroscience Personality Scales	Plieger et al., 2014
Harm avoidance (anticipatory worry, fatigability, & fear of uncertainty)	Temperament Character Inventory	Nyman et al., 2011
Worry	Penn State Worry Questionnaire	Bredemeier et al., 2014
Attentional Bias	Emotional stroop task Dot-probe task Spatial cueing task Visual search task	Bar-Haim et al., 2007

2.1. Endophenotypes of anxiety disorders

One strategy that can aid the identification of genes related to treatment response in GAD is the adoption of an intermediate phenotype, or endophenotype, approach. Thus far, this approach has gained popularity within psychiatric genetic research to establish genes related to the etiology of these disorders. Given the heterogeneous nature of psychiatric disorders, much of the suspension in research advancements is due to the use of diagnoses to find genetic associations (Gottesman and Gould, 2003; LeDoux and Pine, 2016). Strategies that attempt to identify genes related to an anxiety diagnosis are restricting since psychiatric disorders in general are polygenic, diagnoses are not based on objective biological measurements, symptoms often overlap across different disorders, and two patients with the same disorder could have different symptoms (Bas-Hoogendam et al., 2016). Therefore, endophenotypes can be used to elucidate these complex conditions and further our understanding of the genes that play a role in anxiety disorders, including GAD, and treatment response.

An endophenotype is a measurable characteristic that 1) is associated with the disorder in question, 2) is stable and state-independent, existing whether or not the disorder is active, 3) shows heritability, and 4) shows co-segregation with the disorder among families, where the endophenotype is present in non-affected family members to a greater degree compared to the general population (Bas-Hoogendam et al., 2016; Gottesman and Gould, 2003). Essentially, the endophenotype approach breaks down a complex disorder into more homogeneous units that can be measured objectively, with endophenotypes being thought to be the link between particular genes and the disorder (Bas-Hoogendam et al., 2016). Although the endophenotype itself may not necessarily have a simple genetic architecture, the utility of this approach comes from its ability to provide greater insight into the disorder's underlying pathological mechanisms that may be etiological (Bas-Hoogendam et al., 2016). Additionally, given the fact that endophenotype traits tend to be seen before disease onset, genes related to endophenotype presentations have the potential to detect individuals at risk (Bas-Hoogendam et al., 2016). The endophenotype approach has been successfully used by Clementz and colleagues to identify three subtypes of psychosis among patients with schizophrenia, schizoaffective disorder, and bipolar disorder that were outside of the classic diagnostic boundaries (Clementz et al., 2016). To establish these subtypes, the authors investigated several biomarker measures related to neurobiological alterations seen in psychosis, which included assessments of cognitive control and sensorimotor reactivity. The authors also found that their resulting subtypes differed based on brain structure and social functioning. Similarly, six transdiagnostic symptom subtypes have been identified among patients with MDD, panic disorder, and PTSD through measures of mood, anxiety, and stress symptomatology, with these subtypes replicating in an independent sample (Grisanzio et al., 2018). The six subtypes were defined by normative mood (43% of the sample), tension (19%), anxious arousal (13%), general anxiety (9%), melancholia (9%), and anhedonia (7%). In addition, the subtypes differed in measures of cognitive control, working memory, social functioning, emotional resilience, and brain activation. These studies demonstrate the feasibility of using endophenotypes to establish meaningful subtypes that cut across psychiatric diagnoses, which can be used to disentangle overlapping symptomatology and initiate treatments tailored to specific symptom subtypes (Grisanzio et al., 2018). The endophenotype approach is in line with the philosophy of the NIMH Research Domain Criteria (RDoC), which promotes a framework to assess mental disorders using dimensional, rather than categorical, methods (Montalvo-Ortiz et al., 2016; National Institute of Mental Health). The RDoC is particularly valuable in genetic studies of psychiatric disorders, as it outlines six research domains involved in the overarching concept of psychopathology, each consisting of several potential endophenotypes. Genes can therefore be linked with these measurable endophenotypes that underlie psychiatric disorders, rather than promoting the linkage of genes to multifaceted diagnoses (Montalvo-Ortiz et al., 2016). Thus, investigating endophenotypes related to GAD, particularly with the aid of the RDoC initiative, may allow for progress in biomarker identification. See Table 2 for a list of endophenotypes that have been proposed for the study of pathological anxiety. This use of the endophenotype approach to find biomarkers can be extended into PGx studies of GAD through investigating treatment response defined by alterations in GAD-related endophenotypes, or by using genes associated with GAD-related endophenotypes to study GAD treatment response. This approach may demonstrate considerable utility for the attempts to uncover novel genetic treatment response predictors for GAD.

2.1.1. Physiological endophenotypes

Endophenotypes related to anxiety disorder mechanisms have been predominantly investigated through the RDoC's negative valence domain, which includes the constructs of acute threat and potential threat.

The acute threat construct is used to measure fear, and several studies have adapted measures and paradigms related to this construct to evaluate endophenotypes of anxiety disorders that are related to fear or threat responses (Sumner et al., 2016). One measure related to acute threat is the magnitude of the startle reflex. The startle reflex is most often quantified by the eyeblink component of this response, measured with electromyography recordings of the activity of the orbicularis oculi muscle (Grillon and Baas, 2003). This reflex can be assessed either at baseline to determine basic defensive physiology or in response to fearful or anxiety-provoking stimuli (Sumner et al., 2016). The startle reflex is also recognized as a part of the RDoC's potential threat construct of the negative valence domain, and part of the arousal/regulatory and sensorimotor domains. Exaggerated startle reactivity fulfills each of the qualifications of an endophenotype for anxiety disorders, as it has been evidenced in all of the anxiety disorders, exists in children prior to anxiety disorder onset, demonstrates approximately 50% heritability, and is present in non-affected siblings of patients with anxiety disorders (Bakker et al., 2009; Gorka et al., 2017; Grillon et al., 2017; Lissek et al., 2014; Vaidyanathan et al., 2014; Waters et al., 2008). Startle reactivity has also been assessed as a potential biomarker of treatment response within anxiety disorders. Following CBT, startle magnitude decreases in children with anxiety disorders who respond to treatment, but remains unchanged or increases in non-responders (Bakker et al., 2011). Startle reactivity also decreases following exposure therapy in phobic individuals, and those with a larger pre-treatment startle potentiation to phobic cues have poorer treatment response (de Jong et al., 1996; Kashdan et al., 2012). Currently, there is a lack of studies assessing the ability of startle to identify pharmacological treatment responders in patients with anxiety disorders. However, in healthy individuals, acute administration of citalopram increases startle to both fear- and anxiety-provoking stimuli, while 14 days of chronic citalopram reduces startle during contextual anxiety, but not during cued fear (Grillon et al., 2007, 2009). This is in line with the observed clinical anxiogenic side effect during citalopram treatment onset, and efficacy following chronic treatment. Interestingly, patients with MDD tend to show blunted startle reactivity, which is opposite to the startle pattern seen in patients with anxiety disorders, and higher baseline startle magnitude among patients with MDD predicts greater improvement of depression symptoms following antidepressant treatment (Quednow et al., 2004). Therefore, startle reactivity not only demonstrates promise as an endophenotype of anxiety disorders, but also shows potential as a biomarker that can identify treatment responders. It thus follows that future studies should assess whether startle can predict treatment outcomes in GAD and investigate genetic variants associated with startle magnitude variations to determine their utility in predicting GAD treatment responders, which can additionally provide novel insights regarding the mechanisms that induce pathological anxiety.

Another physiological evaluation of acute threat is the carbon dioxide challenge. In this task, the anxiogenic reactions resulting from a single inhalation of a 35% CO_2/65% O_2 gas mixture are assessed (Caldirola et al., 1997; Telch et al., 2012). Individuals with anxiety disorders tend to show increased anxious responses to this task (Caldirola et al., 1997; Telch et al., 2012). Increased sensitivity to this task is also a risk factor for subsequent pathological anxiety, as shown in one study that found that soldiers with increased emotional reactions to this challenge were more likely to develop anxiety and PTSD diagnoses after being exposed to war (Telch et al., 2012). Carbon dioxide hypersensitivity is thus likely another endophenotype of anxiety disorders given the association with diagnosis, its ability to identify those at risk for diagnosis, and the heritability of CO_2-evoked acute anxiety, which ranges from 42% to 57% (Battaglia et al., 2007). Furthermore, lower levels of end-tidal CO_2, which is a biomarker of hyperventilation, during this challenge has been shown to predict poorer CBT response and dropout in patients with anxiety disorders (Tolin et al., 2017). Although there are no studies investigating the ability of response to this task to predict pharmacological treatment outcome for patients with anxiety disorders, medications that have efficacy for treating GAD have been shown to reduce subjective anxiety ratings during this task in both healthy individuals and in individuals with panic disorder (Bailey et al., 2007; Gorman et al., 2004). Therefore, future studies should aim to identify genes that are related to variations in CO_2 sensitivity, which may show promise as biomarkers for treatment response among patients with GAD.

Although the physiological endophenotypes of startle reactivity and CO_2 sensitivity have many advantages over traditional self-report measures given their objective nature, disadvantages of these approaches arise due to the greater time commitments and increased difficulty in the administration of these paradigms compared to self-report questionnaires. As well, there is a limited range of aversive or fear/anxiety-provoking stimuli that can be used in human experiments, especially among individuals with anxiety disorders.

2.1.2. Personality-related endophenotypes

Several other traits that tap into the potential threat construct within the RDoC's negative valence domain have been linked with anxiety disorders and could therefore serve as valuable endophenotypes that can help explain their development (Liu et al., 2017). These traits include anxiety sensitivity (AS), behavioural inhibition (BI), and intolerance of uncertainty (IU), which are measured using self-report with the Anxiety Sensitivity Index, Behavioral Inhibition System scale, and the Intolerance of Uncertainty scale, respectively (National Institute of Mental Health). For example, BI reflects a tendency to display avoidant behaviours when in contact with novel stimuli (Clauss and Blackford, 2012). Given its robust association with anxiety disorders, stable nature, and heritability, BI is considered to be a promising endophenotype of anxiety disorders (Clauss and Blackford, 2012; Frenkel et al., 2015; Maack et al., 2012; Paulus et al., 2015; Smith et al., 2012). Although there are no studies investigating the ability of trait BI to predict subsequent treatment response among patients with anxiety disorders, its promise as an endophenotype warrants search into this possibility. Dimensions within trait AS, namely AS specific to physical concerns and social concerns, showed trends toward association with fluoxetine response in patients with GAD, suggesting that patients with higher levels of these dimensions respond less well to fluoxetine treatment (Olatunji et al., 2008). Higher levels of IU have also been able to predict poorer CBT response among patients with social anxiety disorder (SAD), and the change in IU levels across CBT has been shown to predict the amount of anxiety symptom reduction across treatment (Katz et al., 2017; Stevens et al., 2018).

Although not directly mentioned in the RDoC, other personality-related endophenotypes for anxiety disorders have been identified that are aligned with the negative valence domain. Personality traits are heritable, and are therefore fitting for further endophenotype analysis (Jang et al., 1998). Specifically, the personality trait of neuroticism, as measured with the Eysenck Personality Questionnaire (EPQ) or Neuroticism-Extraversion-Openness Personality Inventory (NEO), is associated with distinct neural correlates in patients with anxiety disorders that differ from healthy individuals (Andreescu et al., 2015). One study using GWAS data found a genetic correlation of 0.86 between anxiety disorder diagnosis and neuroticism (Okbay et al., 2016). These strong biological associations between neuroticism and anxiety disorders suggest that neuroticism is a prominent feature in individuals with anxiety disorders, thus implicating it as an important endophenotype. Furthermore, patients with GAD who are low in trait neuroticism demonstrate greater improvements to pharmacotherapy, and higher baseline neuroticism is associated with poorer response to CBT and acceptance and commitment therapy across anxiety disorders (Rickels et al., 1993; Wolitzky-Taylor et al., 2012). This therefore attests to the ability of this trait to identify GAD treatment responders, or those at risk of poor response. An additional anxiety-related personality facet that shares a correlation with genes involved in anxiety disorders is

extreme response style, which suggests it could be another potential endophenotype (Plieger et al., 2014). This trait is defined as a tendency to endorse extreme options on Likert scales (Plieger et al., 2014). Extreme response style is measured using the NEO inventory, Temperament Character Inventory (TCI), or Affective Neuroscience Personality Scales (ANPS) (Plieger et al., 2014). There are currently no studies investigating treatment response in patients with anxiety disorders using this trait, however, among those with depression, higher levels of extreme responses that are positive in nature predict relapse and recurrence of depressive symptoms following antidepressant or cognitive therapy (Forand and DeRubeis, 2014).

Harm avoidance is another personality trait that is measured with the TCI (Nyman et al., 2011). The harm avoidance trait, as well as the subscales of anticipatory worry, fatigability, and fear of uncertainty, have strong positive correlations with anxiety symptoms (Nyman et al., 2011). Furthermore, genetic variants such as rs6265 in *BDNF* and rs4680 in *COMT* that have been associated with higher scores in the anticipatory worry and fear of uncertainty subscales have also been associated with GAD diagnosis and treatment response (Gottschalk and Domschke, 2017; Narasimhan et al., 2012). Harm avoidance has been associated with varied treatment outcomes among patients with anxiety disorders, with low initial harm avoidance being associated with greater improvements following CBT or psychodynamic therapy combined with pharmacotherapy (Ociskova et al., 2016). The construct of worry can also be evaluated using the Penn State Worry Questionnaire (PSWQ), and this construct has been used as a measure of treatment outcome in GAD (Beesdo-Baum et al., 2012). One genetic study on this measure of worry has identified an interaction effect between 5-HTTLPR and rs6265 in *BDNF*, in which the presence of short alleles from 5-HTTLPR predict increased PSWQ scores, but only among *BDNF* Met allele carriers (Bredemeier et al., 2014). Therefore, each of these personality-related studies establish additional promising endophenotypes for anxiety disorders that may aid the discovery of novel markers of treatment response for GAD.

2.1.3. Attention-related endophenotypes

Another potential endophenotype for anxiety disorders stems from executive function deficits that are related to the RDoC construct of attention within the cognitive systems domain. Specifically, individuals with anxiety disorders tend to show that their attention is biased towards threatening stimuli, which can be measured using many paradigms including the emotional stroop, dot-probe, spatial cueing, and visual search tasks (Cisler and Koster, 2010). Importantly, biases showing attention to threats have been found using all of these paradigms, and these biases have been seen across anxiety disorders, suggesting that attentional bias is a robust characteristic associated with pathological anxiety, and therefore a strong candidate endophenotype for anxiety disorders (Bar-Haim et al., 2007; Cisler and Koster, 2010). Assessments of the ability of attentional bias measures to predict pharmacological treatment response in patients with anxiety disorders are lacking. However, in regard to response to CBT, patients with SAD that show greater attention towards threat and those that are slower at disengaging from happy faces have worse treatment outcomes (Byrow and Peters, 2017). Also, older adults with GAD experience a marginally significant reduction in bias towards threatening words after CBT (Mohlman et al., 2013). The evidence that measures of attentional bias can be altered by treatment and predict outcome suggests that these measures may show promise for the identification of patients with GAD that respond to pharmacological treatment.

2.2. Imaging genetics

Overall, the neuroimaging literature demonstrates similarities between neural activation patterns in GAD and other anxiety disorders, but also informs the unique nature of patients with GAD to have anxiety across contexts rather than necessitating specific cues or situations to induce anxiety. Neuroimaging has also shown utility in the prediction of treatment response among patients with GAD (McClure et al., 2007; Nitschke et al., 2009; Whalen et al., 2008). Given the stimulus-independent nature and heterogeneity of neurocircuitry underlying GAD, it would be beneficial to provide other measures to inform imaging results, such as the incorporation of genetics. This incorporation is the imaging genetics approach, in which particular neural activation patterns can serve as further endophenotypes for GAD that can inform etiological investigations as well as predict treatment response. Currently, there are few studies on GAD that directly incorporate both imaging and genetics. In a candidate gene study (n = 50), patients with GAD that have low expression variants of 5-HTTLPR and rs25531 from *SLC6A4* display reduced activity in the amygdala and anterior insula when anticipating and responding to aversive images (Oathes et al., 2015). Furthermore, while there is a lack of imaging genetic studies on GAD, there are several studies that link polymorphisms in candidate genes with neural activation patterns that have been previously found in GAD. For instance, studies have found associations between heightened amygdala reactivity and several genetic variants including the short allele of the 5-HTTLPR variant in *SLC6A4*, the T-allele of rs4570625 in the tryptophan hydroxylase 2 (*TPH2*) gene, lower expression variants of the *MAOA* gene, CC carriers of *HTR1A*, the Met allele of *BDNF*, and the T-allele of rs324981 in *NPSR1* (Sumner et al., 2016). Therefore, neuroimaging, along with supplemental genetic methods, can increase the validity of particular neural activation patterns as endophenotypes for GAD that future studies can use to provide insights on etiology and predict treatment response.

2.3. Anxiety and epigenetics: animal models

Given that anxiety disorders are associated with only moderate heritability estimates, the environment must play a substantial role in their onset (Bartlett et al., 2017). However, despite the clear influence of the environment in anxiety manifestations, investigations of epigenetic alterations in human brains are challenging due to a lack of accessible human brain tissue that forces researchers to use peripheral tissues such as blood and epithelial cells that may not be equivalent to changes occurring at the level of the brain (Bartlett et al., 2017). Consequently, animal models are used to delineate anxiety-related epigenetic changes. These animal models have used paradigms to measure anxiety-like behaviours following the induction of acute or chronic stressors (Schiele and Domschke, 2018). Several studies have imposed these environmental stressors during different windows of time, either during the prenatal period, early life, or adulthood. These studies using different perturbation times have yielded several alterations in the epigenome among various brain regions in animal models (see Table 3). For example, animals exposed to stress prenatally exhibit anxiety-like behaviour and larger hypothalamic-pituitary-adrenal (HPA) axis reactivity and stress sensitivity, which is further associated with increased expression of the corticotropin-releasing hormone gene (*Crh*) and decreased expression of the glucocorticoid receptor gene (*Nr3c1*) (Bartlett et al., 2017; Mueller and Bale, 2008; Xu et al., 2014). Decreased expression of the gene *reelin* in the PFC in offspring exposed to prenatal restraint stress is also observed, with these rodents further displaying elevated anxiety levels and deficits in learning and memory consolidation (Palacios-Garcia et al., 2015). MicroRNA (miRNA) expression is also altered by prenatal stress, as shown by the reductions of miR-332, miR-574, and miR-873 in the male brains of second generation offspring of fathers that had mothers that were subject to chronic variable stress, with the offspring also showing elevated stress sensitivity (Morgan and Bale, 2011). Each of these studies support the hypothesis that stress during pregnancy may create lasting changes that are passed on to offspring, making them more prone to exhibiting pathological anxiety. Similarly, studies inducing early life stressors, such as exposure of pups to mothers that provide poor rearing conditions, consistently provide evidence that epigenetic changes are associated

Table 3
Gene expression and epigenetic changes observed in animal models of anxiety.

Perturbation Time	Gene	Epigenetic Findings[a]	Perturbation Type	Brain Area	Rodent Sex		Study
					Male	Female	
Prenatal	*Crh*	↓ methylation ↑ expression	Chronic variable stress	Hypothalamus & Amygdala	✓	×	Mueller and Bale, 2008
	Nr3c1	↑ methylation ↓ expression		Hypothalamus Hippocampus			
	Crh	↓ methylation ↑ expression	Restraint stress	Hypothalamus	✓	✓	Xu et al., 2014
	Reelin	↑ methylation ↓ expression	Restraint stress	Cerebral cortex	✓	✓	Palacios-Garcia et al., 2015
Early Life	*Nr3c1*	↑ methylation ↓ acetylation ↓ expression	Poor rearing conditions	Hippocampus	✓	✓	Weaver et al., 2004
	Erα1b	↑ methylation ↓ expression	Poor rearing conditions	Medial Preoptic Area	-	✓	Champagne et al., 2006
	Gad1	↑ methylation ↓ acetylation ↓ expression	Poor rearing conditions	Hippocampus	✓	-	Zhang et al., 2010
	Dnmt1	↑ expression					
	Bdnf	↑ methylation ↓ expression	Poor rearing conditions	PFC	✓	✓	Roth et al., 2009
	Crh	↓ methylation ↑ expression[b]	Maternal separation	Hypothalamus (Paraventricular nucleus)	✓	✓	Chen et al., 2012
	Reelin	↑ methylation ↓ expression	Maternal separation	Hippocampus	✓	-	Qin et al., 2011
	Ntsr1	↑ methylation ↓ expression	Maternal separation	Amygdala	✓	-	Toda et al., 2014
	Pomc	↓ methylation ↑ expression	Maternal separation	Pituitary	✓	-	Wu et al., 2014
	Crfr2	↓ methylation ↓ expression	Maternal separation	Sperm from caudal epididymis in males and cortex in females	✓	✓	Franklin et al.. 2010
	Mecp2	↑ methylation ↓ expression					
	Cb1	↑ methylation ↓ expression					
	Avp	↓ methylation ↑ expression	Maternal separation	Hypothalamus (Paraventricular nucleus)	✓	-	Murgatroyd et al., 2009
	Avp	↑ methylation	Maternal separation	Hippocampus	✓	-	Kember et al., 2012
	Nr3c1	↑ methylation					
	Nr4a1	↓ methylation					
	Syn1	↑ methylation[c] ↓ expression	Maternal separation	Amygdala	✓	✓	Park et al., 2014
	Src	↓ methylation[c] ↑ expression					
	Skap1	↓ methylation[c] ↑ expression					
	Map4k2	↓ methylation[c] ↑ expression					
	Prkag1	↓ methylation[c] ↑ expression					
	Map4k1	↓ methylation[c] ↑ expression					
	Cdk5	↑ methylation[c] ↓ expression					
	Srd5a1	↑ methylation ↓ expression	Juvenile social isolation	PFC	✓	-	Araki et al., 2015
	Crhr1	↑ methylation ↑ expression	Chronic mild stress	Amygdala	✓	-	Sotnikov et al., 2014
	Fkbp5	↓ methylation[d] ↑ expression	Chronic corticosterone administration	Hypothalamus Hippocampus Blood	✓	-	Lee et al., 2010
	Nr3c1	↓ expression		Hippocampus Blood			
	Hsp90	↓ expression		Blood			
	Crh	↓ expression		Hypothalamus Hippocampus			

(*continued on next page*)

Table 3 (*continued*)

Perturbation Time	Gene	Epigenetic Findings[a]	Perturbation Type	Brain Area	Rodent Sex		Study
					Male	Female	
Adulthood	*Crh*	↓ methylation ↑ expression	Social defeat	Hypothalamus (Paraventricular nucleus)	✓	-	Elliott et al., 2010
	Hdac2	↓ expression					
	Dnmt3b	↓ expression					
	Gadd45b	↑ expression					
	Bdnf	↑ histone methylation ↓ expression	Social defeat	Hippocampus	✓	-	Tsankova et al., 2006
	Dnmt3a/3b	↑ expression	Fear conditioning	Hippocampus	✓	-	Miller and Sweatt, 2007
	c-fos	↑ expression					
	Pp1	↑ methylation ↓ expression					
	Reelin	↓ methylation ↑ expression					
	Hdac5	↑ expression	Chronic unpredictable stress	Hippocampus	✓	-	Liu et al., 2014
	H3k9	↓ acetylation					
	H4k12	↓ acetylation					
	Th	↓ expression					
	Tph	↓ expression					

✓ = Present and significant; × = Present and not significant; - = not included.
[a] Methylation status determined in promoter region.
[b] Change in hnRNA, not mRNA.
[c] Methylation change observed in transcription start site.
[d] Methylation change observed in intron 1 (blood) and 5 (hypothalamus and hippocampus).

with the anxiety-like behavioural alterations that are observed (see Table 3). Exposure of rodents to stressors in adulthood, such as social defeat stress, also produces anxiety-like behaviours (Elliott et al., 2010). Social defeat increases mRNA expression of *Crh* in the hypothalamus with defeated rodents demonstrating anxiety-like behaviours, while rodents that show resilience to social defeat do not show these changes (Elliott et al., 2010). Socially defeated mice also have decreased expression of histone deacetylase 2 (*Hdac2*) and DNA methyltransferase 3 beta (*Dnmt3b*), while growth arrest and DNA damage inducible beta (*Gadd45b*), a gene that induces demethylation of promoter regions in genes like *Crh*, shows increased expression (Elliott et al., 2010). Socially defeated mice also show decreased expression with associated increases in histone methylation at *Bdnf* gene promoters in the hippocampus (Tsankova et al., 2006). This downregulation of expression is reversed by the antidepressant imipramine, which also increases histone acetylation at the *Bdnf* promoter, downregulates *Hdac5*, and leads to a reduction in defeat behaviours (Tsankova et al., 2006).

In summary, each of the epigenetic studies in animal models of anxiety emphasize the moderating role of epigenetic processes in anxiety-related responses to chronic stressors in the environment. Given the considerable role that stress plays in anxiety disorders, it is possible that this animal research could be transferred to human research. However, although animal models of anxiety have been greatly valuable for gathering biological insights of anxiety states, the question remains as to the true transferability of such subjective states that can only be inferred through behavioural measurements in animals (Steimer, 2011). There is also the complication that animal models are designed to create states of anxiety that are considered extreme, but still normal and adaptive given the circumstances of the experiment (Steimer, 2011). These models are therefore not investigating anxiety pathology per se. One potential pathway forward is to investigate human anxiety-related endophenotypes in animal epigenetic studies, as these endophenotypes are often quantitative and physiological, rather than being exclusively behavioural and inferential (Lampis et al., 2011). Furthermore, considering that most of the studies focus on DNA methylation in a known small number of candidate genes, genome-wide analyses along with introducing antidepressants in animal models and assessing the behavioural and associated epigenetic changes may shed light into novel epigenetic predictors of treatment response that can be studied in humans.

2.4. Polygenic risk scores

Considering that genome-wide association studies have not been particularly successful in identifying genetic factors associated with response to psychotropic medications, alternative genetic strategies need to be implemented. Treatment response, similar to GAD diagnosis, is a complex polygenic trait where thousands of SNPs with small effects are expected to contribute to its heritability. Moreover, common genetic variants have been shown to explain 42% of the variance in antidepressant response in MDD patients of European ancestry (Tansey et al., 2013). Polygenic risk score (PRS) has emerged as an approach where the genome-wide variation is aggregated and can be used to investigate its combined predictive power in a new validation sample of the same disease or to identify genetic overlap with different traits/disorders. PRS is typically calculated as a weighted sum of the risk alleles exceeding a certain p-value threshold, weighted by their association coefficients identified typically from a GWAS (Euesden et al., 2015). This technique was first employed in a schizophrenia GWAS and showed that the risk of schizophrenia is polygenic and overlaps with bipolar disorder but not with several non-psychiatric diseases (International Schizophrenia et al., 2009). Since then, PRS has been used to establish genetic overlap between several diseases including anorexia nervosa and schizophrenia, anorexia and obesity, and depression and cardiovascular disorder (Bulik-Sullivan et al., 2015; McCoy et al., 2017). PRS has also been correlated with severity of symptoms, prefrontal activity, brain structures, and reduction in cortical volumes among others. In terms of antidepressant treatment response, PRSs from MDD and schizophrenia did not significantly predict treatment efficacy (Garcia-Gonzalez et al., 2017). More recently, Zwicker et al. observed that a higher PRS for c-reactive protein levels was associated with slightly greater response to escitalopram and poorer response to nortriptyline in MDD patients (Zwicker et al., 2018). Similarly, the PRSs for the personality traits of openness and neuroticism were associated with remission after four weeks of SSRI treatment in two independent cohorts (Amare et al., 2018). These studies give credence to the utility of PRS in identifying responders to antidepressant treatment. The association of the PRS for personality traits with remission is noteworthy as previous clinical studies have demonstrated their significant effect on antidepressant response and

remission. For example, in patients with MDD, lower neuroticism and higher extraversion and openness were observed in responders compared to non-responders to treatment with medication or psychotherapy (Bagby et al., 2008; Quilty et al., 2008). Measuring all of the factors, such as personality along with symptom dimensions, that may influence treatment response is challenging. Therefore, strategies such as the use of PRS which can serve as a surrogate for these factors can be used to identify treatment responders. This can potentially obliterate the need to perform these measurements. Thus, PRSs from studies of personality traits, subjective well-being, schizophrenia, MDD, and anxiety disorders, individually or in a combined model, might be useful in identifying individuals that may respond to treatment.

3. Summary and future directions

While current genetic, pharmacogenetic, pharmaco-epigenetic, and neuroimaging research provide promising results, there still remains an overall lack of biomarker investigations, especially related to treatment response, for GAD. This review therefore puts forth suggestions that can advance this research and ultimately aid the establishment of greater precision of treatment selection and improved treatment outcomes. Specifically, 1) the use of endophenotypes rather than diagnoses to identify genetic variants associated with treatment response, 2) the incorporation of genetics into neuroimaging studies designed to predict treatment outcomes in GAD, 3) the exploration of genes identified in animal epigenetic studies in humans, and 4) the use of PRS to identify treatment responders might be useful strategies to find markers predicting treatment outcomes in patients with GAD. Identification of factors that predict treatment response will reduce trial-and-error switches of medications and decrease the suffering of patients and their families. This will ultimately lead to savings of millions of health care dollars due to the reduction of ineffective or harmful prescriptions, treatment non-compliance, and unnecessary hospitalizations.

Conflicts of interest

JLK is a member of the Scientific Advisory Board of Myriad Neuroscience (unpaid) and holds several patents relating to pharmacogenetic tests for psychiatric medications. The remaining authors have no conflicts of interest to disclose.

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