Biological predictors of pharmacological therapy in anxiety disorders

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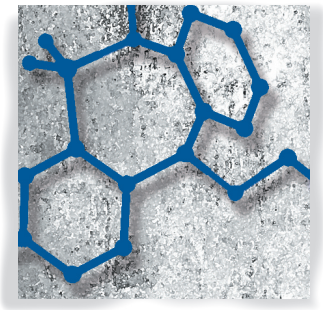

At least one third of patients with anxiety disorders do not adequately respond to available pharmacological treatment. The reason that some patients with anxiety disorders respond well, but others not, to the same classes of medication is not yet fully understood. It is suggested that several biological factors may influence treatment mechanisms in anxiety and therefore could be identified as possible biomarkers predicting treatment response. In this review, we look at current evidence exploring different types of treatment predictors, including neuroimaging, genetic factors, and blood-related measures, which could open up novel perspectives in clinical management of patients with anxiety disorders.

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Introduction

Anxiety disorders, including generalized anxiety disorder (GAD), panic disorder (PD), social anxiety disorder (SAD), simple phobias (SP), obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD), are the most common psychiatric illnesses experienced, affecting an estimated 18% of people in the United States, according to epidemiological studies.[1] Although both OCD and PTSD are still considered by many to be anxiety disorders and have been classified as such in the past, they have been removed from the category in the most recent (5th) edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* and are now described in different chapters (Obsessive-Compulsive and Related Disorders and Trauma and Stressor-Related Disorders, respectively).[2] The age of onset of anxiety disorders is usually in the mid-twenties, and women are twice as likely as men to be diagnosed with an anxiety condition, but how much of this sex difference is due to socioeconomic factors has not been established.[3] In additional, anxiety disorders are char-

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acterized by a chronic and fluctuating clinical course, and can be seriously disabling diseases causing impairment in social, personal, and occupational functioning, as well as leading to significant loss in quality of life and to an enormous social cost.[4] As demonstrated in recent studies, the anxiety disorders are the most costly in the USA, amounting to $46.6 billion, or 31.5% of the total economic costs of mental disorders.[5] Therefore, the treatment of these disorders is one of the current problems in medicine today.[6] In community studies, patients with anxiety disorders were found to use more medical and psychiatric services than control populations.[7] The availability of more effective, relatively low-cost outpatient treatment could substantially reduce the economic and social burden of these common and often crippling disorders.[8]

Nevertheless, anxiety disorders are notoriously difficult to successfully treat, and a variety of genetic and environmental factors contribute to their development and severity.[9] The importance of an improved approach to treating anxiety is highlighted by the inconsistent results seen with the classes of drugs considered to be the contemporary first-line treatment: selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). Although these agents have been shown to be beneficial for the treatment of certain anxiety disorders, not all patients achieve an adequate clinical therapeutic response. For example, in a 3-year follow-up only 10% of patients with PD were symptom-free[10] and only 12% of PD patients were in full remission after 5 years.[11] The existence of "nonresponders" indicates that SSRIs and SNRIs are not the failsafe solution to treating anxiety that clinicians have been looking for.[3] In addition, SSRIs and SNRIs are associated with complications that can limit their use in some patients, including delays in producing the desired clinical reduction in anxiety or even potential worsening of the anxiety particularly at the start of treatment leading to dropouts.[12] Other issues include the risk for discontinuation syndromes in noncompliant patient populations. Furthermore, some SSRIs (eg, citalopram) are not suitable for patients with heart problems.[13] Another class of drugs, benzodiazepine (BZD) anxiolytics, has played a central role in the pharmacologic management of anxiety disorders for about 50 years. Although not as widely prescribed as in the past, these compounds nevertheless remain an effective alternative to SSRIs; however, the chronic usage of BZDs is strongly restricted in clinical practice due to dependence risk.[14]

All things considered, the antidepressants, and first of all the SSRIs, are more preferable pharmacological agents in treatment of anxiety disorders, even if a substantial proportion of patients are not achieving significant improvement and remission during medication. Also it is rather difficult in routine practice to predict which patients will respond well to a pharmacological treatment and which will not. So similarly to in depression, treatment in patients with anxiety disorders is usually chosen on an empirical basis, where clinical approaches are largely trial and error, and when the first treatment does not result in recovery for the patient, there is little proven scientific basis for choosing the next.[15] Once treatment has begun, an improvement in clinical symptoms early in the course of therapy generally points towards an eventual good treatment response. However, in most cases, efficacy needs to be evaluated after 6 to 12 weeks of treatment, and a large proportion of patients have persistent symptoms despite a full treatment trial.[16] Current treatment guidelines recommend that an initial treatment be tried for long enough a period to determine how much it will benefit a patient.[15] On average, at least 4 weeks are needed to attain response, and 6 weeks to attain remission during treatment with an initial SSRI antidepressant, but remission can take 12 weeks or longer.[17] Because most patients fail to enter remission with the first antidepressant prescribed,[17] they then commonly enter a period of serial trial-and-error treatments using switches between, or combinations of, medications.[18] Typically it can take 1 year or more to hit upon a successful treatment.[19,20] It is not surprising that using this "hit-or-miss" approach, 26% of those who fail to improve with the first treatment simply stop taking their medication, frequently within the first 2 weeks,[21] and up to 42% of patients discontinue medication within the first 30 days.[22] Also, this unsuccessful use of antidepressants significantly increases the total cost of treatment that in its turn significantly worsens the overall socioeconomic condition.

There are a vast number of studies that have sought to identify predictors of response to antidepressant medication. Putative predictors include demographic and clinical characteristics, personality traits, biological markers, and psychophysiological features.[23,24] Overall, these studies have not as yet yielded findings that were robust enough to be clinically relevant.[25,26]

However, there is strong belief that further search for biological predictors of treatment response, which are also defined as "treatment biomarkers," would contribute to the personalized medicine approach, in which biomarkers would guide decision making and help to select the most suitable medication for individual patients. Moreover, incorporation of predicting biomarkers into antidepressant treatment algorithms could speed recovery from disease by shortening or eliminating lengthy and ineffective trials.[15] During the last decade there has been intensive ongoing research of biomarkers predicting treatment outcome of antidepressants. To date, the majority of this research was conducted in patients with depression, and there are only a small number of published studies in which treatment biomarkers were explored in patients with any anxiety disorder, which means that biomarker discovery is still on very early stage in anxiety field. Taken into account that the same antidepressant groups, like SSRIs and SNRIs, are highly effective in both depression and anxiety, we will focus here on available data and promising findings from treatment biomarker research in both clinical conditions. Also, keeping in mind that the aforementioned antidepressants may have similar or overlapping treatment mechanisms in depression and anxiety, we suggest that current achievements in biomarker discovery in depression could be applicable for further research in anxiety disorders and may improve our understanding about perspectives in this important area. It should, however, be noted that at the present time none of the biomarkers have sufficiently proven utility to be ready for clinical application, due to their low sensitivity and specificity.[27] Nevertheless, the several classes of biomarkers, including brain structural or functional findings, as well as genomic, proteomic, and metabolomic measures, have been identified by previous research, whereas some of them have shown clear promise for predicting treatment response.[15] So, we will review the available evidence supporting the use of different types of treatment predictive biomarkers. For a simplified summary, the key findings are summarized in *Table I*.

Sample	Treatment	Predictor	Outcome	Reference
Neuroimaging biomarkers				
PTSD (n=39)	CBT (12w)	Greater right Hip	Response	40
PTSD (n=13)	CBT (8w)	Larger rACC	Response	41
PTSD (n=30)	CBT (36)	Right sACC	Response	42
OCD (n=14)	SSRI (12w)	Smaller right mlOFC	Response	46
OCD (n=15)	CBT (12w)	Larger right mPFC		
OCD (n=15)	Surgery	ACC	Response	47
PD (n=21)	SSRI (6w)	Total GMV	Response	43
PD (n=49)	CBT (12w)	BOLD in ACC-Amy	Response	55
PD (n=14)	CBT (4w)	Increased BOLD in insula and dlPFC	Response	57
PD (n=23) GAD (n=25)	CBT (10w)	Greater BOLD in cortico-limbic circuitry	Response	58
GAD (n=15)	SNRI (8w)	Greater BOLD in ACC and lower in Amy	Response	59, 60

Table I. Summary of positive findings for treatment biomarkers in anxiety disorders. ADs, antidepressants; CBT, cognitive behavioral therapy; PE, prolonged exposure therapy; BEP, brief eclectic psychotherapy; w, week; Hip, hippocampus; ACC, anterior cingulate cortex; pgACC, pregenual ACC; rACC, rostral ACC; sACC, subgenual ACC; mlOFC, middle lateral orbitofrontal cortex; mPFC, medial prefrontal cortex; GMV, gray matter volume; dlPFC, dorsolateral prefrontal cortex; BOLD, blood-oxygen-level dependent; OFC, orbitofrontal cortex; iPL, inferior parietal lobe; vACC, ventral anterior cingulate cortex; VFC, ventral frontal cortex; sTG, superior temporal gyrus; TC, temporal cortex; midFC, mid frontal cortex; vmPFC, ventromedial prefrontal cortex; PCC, posterior cingulate cortex; rCBF, regional cerebral blood flow; rCMRGlc, regional glucose metabolism; 99mTc-HMPAO, 99mTc-hexamethylpropyleneamineoxime; 5-HTT, serotonin transporter; 5-HTR1A, serotonin receptor 1A; 5-HTR2A, serotonin receptor 2A; RGS2, regulator of G-protein signaling 2; PACAP, the pituitary adenylate cyclase-activating peptide; CRHR1, corticotropin-releasing hormone receptor 1; DRD3, dopamine receptor D3; NR3C1, nuclear receptor subfamily group C, member 1; PDE1A, phosphodiesterase 1A; DISP1, dispatched homolog 1; GRIN2B, glutamate receptor subunit epsilon-2; PCDH10, protocadherin 10; GPC6, glypican 6; DHEA, dehydroepiandrosterone; BDNF, brain-derived neurotrophic factor; OCD, obsessive-compulsive disorder; PD, panic disorder; PTSD, post-traumatic stress disorder; GAD, generalized anxiety disorder; Amy, amygdala

Neuroimaging

Many of the major advances in biomarker research have arisen from advances in neuroimaging technology, including structural (magnetic resonance imaging [MRI], diffusion tensor imaging [DTI]), functional (functional magnetic resonance imaging [fMRI], positron emission tomography [PET]/single photon emission computed tomography [SPECT], biochemical (magnetic resonance spectroscopy [MRS]), and neurophysiological (electroencephalography [EEG] and magnetoencephalography [MEG]) methodologies.[28] These different neuroimaging techniques have all been used to study whether baseline, pretreatment charac-

Sample	Treatment	Predictor	Outcome	Reference
SAnD (n=21)	CBT (12w)	Greater BOLD in Amy-pgACC	Response	62
PTSD (n=21)	SSRI (12w)	BOLD in precuneus and OFC	Response	65
PTSD (n=41)	CBT (32w)	Greater BOLD in left iPL	Response	66
PTSD (n=13)	CBT (8w)	Greater BOLD in Amy-vACC	Non-response	41
OCD (n=25)	SSRI (16w)	BOLD in right VFC	Response	67
OCD (n=17)	SSRI (12w)	BOLD in left sTG	Response	68
PD (n=15)	SSRI (12w)	Global cortical rCMRGlc	Response	75
SAD (n=72)	SSRI (8w)	rCBF in Amy, dlPFC and rostral ACC	Response	76
SAD (n=15)	SSRI (8w)	Higher rCBF in left TC and left midFC	Non-response	77
SAD (n=12)	Tiagabine (6w)	Lower rCMRglu in vmPFC	Response	78
OCD (n=30)	SSRS (24w)	Global change in rCBF	Response	79
OCD (n=15)	SSRS (12w)	Higher whole brain 99mTc-HMPAO	Response	80
OCD (n=9)	SSRS (12w)	Higher rCBF in PCC and lower in OFC	Response	81
Genetic biomarkers				
PD (n=92)	SSRI (12w)	5-HTTLPR LL	Response	99
PD (n=102)	SSRIs (6w)	5-HTR1A -1019 GG	Response	100
PTSD (n=330)	SSRI (12w)	5-HTTLPR LL	Response Low dropout	101
SAD(n=32)	SSRI (12w)	5-HTTLPR LL	Response	102
SAD (n=346)	SSRI (10w)	RGS2 SNPs	Response	104
GAD (n=112)	SNRI (24w)	PACAP rs2856966 A	Response	105
GAD (n=112)	SNRI (24w)	5-HTTLPR LL	Response	107
GAD (n=156)	SNRI (24w)	5-HTR2A rs7997012 G	Response	109
GAD (n=164)	SNRI (6-12w)	CRHR1; DRD3; NR3C1; PDE1A	Response	111
OCD (n=184)	Various ADs (>10w)	CYP2D6 non-extensive	Number of failed trials	121
OCD (n=804)	SSRIs	DISP1; GRIN2B, PCDH10; GPC6	Response	122
Blood-based biomarkers				
PTSD (n=21)	BEP (16w)	Increased DHEA	Response	116
PTSD (n=28)	PE (12w)	Decreased cortisol	Non-response	117
OCD (n=19)	SSRI (8w)	Higher whole-blood serotonin	Response	118
PD (n=22)	SSRI (12w)	Lower beta-adrenoceptor affinity	Non-response	119
PD (n=42)	CBT (10w)	Lower BDNF	Non-response	120

Table I. Continued

teristics, or changes in brain functioning and metabolism correlate with symptom improvement following antidepressant treatment.[27] For example, the structural brain imaging studies have demonstrated usefulness as pretreatment predictors of antidepressant treatment outcome.[15] Recent meta-analyses of structural neuroimaging studies indicate that depressed patients have reduced gray matter volume (GMV) in multiple areas, including the anterior cingulate cortex (ACC) ,[29] subgenual cingulate cortex,[30] and hippocampus.[31] The most robust evidence is for the hippocampus, for which larger volumes predicted better response after 8 weeks of pharmacotherapy in two separate samples.[32,33] In addition, the GMV in the ACC and posterior cingulate cortex was also predictive of clinical remission following 8 weeks of fluoxetine treatment.[34] In 1997 Mayberg et al[35] reported, using PET, that responders to antidepressant treatment showed increased anterior cingulate metabolism at baseline relative to nonresponders and to healthy controls. The diffusion tensor imaging is another relatively novel method, which applies the structural integrity of the fiber tracts between affected neural areas and has predictive potential for delineating treatment responders. For example, depressive nonresponders to 12 weeks of citalopram[36] or escitalopram treatment[37] showed a greater prevalence of microstructural abnormalities in white matter pathways connecting the cortex with limbic and paralimbic areas such as the anterior cingulate. Other studies have also demonstrated that the integrity of these corticolimbic pathways is adversely impacted by adverse life events[38] as well as genetic polymorphisms (eg, 5-HTTLPR).[39] Despite being based on straightforward quick and simple methodology, only a few structural MRI studies have been designed to explore brain markers of therapeutic response in anxiety disorders. Even those available have mostly applied psychotherapy interventions rather than pharmacological medication and did not directly aim to identify structural brain predictors of the treatment outcome. In part this may reflect the fear that many patients with anxiety disorders have for the confined space of the MRI scanner. However, when studies have been conducted they have been informative. For example, structural MRI studies in PTSD have reported that better response to cognitive behavioral therapy (CBT) is predicted by greater right hippocampal GMV[40] and larger rostral ACC volume.[41] Both regions are linked to threat processing and fear memory activation, and seem to be involved in mediation of CBT effectiveness. The other study in PTSD showed that symptom improvement was correlated with, and predicted by, cortical thickness in the right subgenual ACC.[42] Recently, the relatively small studies in patients with PD have demonstrated that remission following 6 weeks of escitalopram treatment is accompanied by both significant increase in the GMV in the left superior frontal gyrus, but reduction in the right precentral gyrus. Furthermore, the changes in total GMV after remission were correlated with changes in clinical scores.[43] Another study using DTI found increased white matter micro-structural integrity reflected by fractional anisotropy in some regions of right uncinate fasciculus and left fronto-occipital fasciculus after escitalopram remission in PD patients.[44] Earlier, increases of GMV were showed in left infero-frontal cortex, right fusiform gyrus, and right cerebellum areas in remitted depressive patients with comorbid PD following 6 weeks' medication with duloxetine.[45] None of these studies have specifically focused on a predictive effect of brain structural measures on treatment response. The only study to do this was that of Hoexter et al[46] who investigated structural MRI correlates as potential pretreatmentbrain markers to predict treatment response in treatment-naïve OCD patients, entering a randomized 12-week clinical trial of either fluoxetine or group-based CBT. This study showed that symptom improvement in the fluoxetine treatment group was significantly correlated with smaller pretreatment GMV within the right middle lateral orbitofrontal cortex (OFC), whereas symptom improvement in the CBT treatment group was significantly correlated with larger pretreatment GMV within the right medial prefrontal cortex (mPFC). Although, these findings suggest that pretreatment GMV of distinct brain regions within the lateral OFC and mPFC were differentially correlated with treatment response to fluoxetine versus CBT in OCD patients, the included sample was quiet small and needs replication in larger sets of patients with a prospective design. Additional data is provided by Banks et al[47] who revealed features of ACC structure and connectivity that predict clinical response to dorsal anterior cingulotomy for refractory OCD. They suggested that the variability seen in individual responses to a highly consistent, stereotyped procedure may be due to neuroanatomical variation in the patients.

The functional MRI (fMRI) approaches, including task-related and resting-state methods, can provide an additional and more comprehensive view on involvement of anxiety neurocircuits in prediction of treatment outcome. The fMRI measures of neuronal activity in mood-regulating pathways were successfully used in studies exploring brain functional predictors of response to antidepressant medication. For example, Anand et al[48] were the first to show that reduced corticolimbic connectivity in depression recovers during the course of treatment and may thus predict antidepressant medication response. The studies, which applied the measure of neuronal response to an emotional task, like processing of facial expressions, also identified that baseline neural reactivity can be used as predictors of treatment outcome. So, increased baseline neuronal reactivity found in depressive patients seems to normalize after successful antidepressant pharmacotherapy[49,50] and CBT.[51] Also particularly the deficient connections between the amygdala and anterior cingulate have been found to be ameliorated after 8 weeks of fluoxetine administration,[52] and another study showed that the changes in task-related reactivity were complementary to differences between treatment responders and nonresponders in resting-state connectivity within corticolimbic circuits.[53] A recent fMRI study with a large enough sample of patients with PD comorbid with agoraphobia has failed to find any brain regions predictive of CBT outcome.[54] However, earlier Leuken et al[55] observed that treatment response to CBT in panic patients was associated with an inhibitory functional coupling between the anterior cingulate cortex and the amygdala, whereas responders and nonresponders were characterized by distinct neuronal activation at baseline time. Their later study in the same sample has demonstrated that inhibitory ACC-amygdala coupling during fear conditioning was associated with the long variant of the 5-HTTLPR polymorphism in PD responders only. This points toward potential intermediate connectivity phenotype modulating response to exposure-based CBT.[56] A better response to brief CBT was predicted by increased pretreatment activation in bilateral insula and left dorsolateral prefrontal cortex (dlPFC) during threat processing in a recent study by Reinecke et al.[57] In addition, the greater activation in cortico-limbic circuitry, including superior frontal gyri, anterior insula, superior temporal and supramarginal gyri and hippocampus, predicted better CBT response in mixed samples of patients with PD and GAD.[58] Regarding pharmacological intervention in PD, the remission following escitalopram treatment was associated with changes in regional homogeneity of temporoparietal regions in a recent fMRI study, which, however, did not specifically explore predictive measures of treatment response.[43] Pharmaco-fMRI research has not been very fruitful, but there is some evidence in small samples of patients with GAD that greater levels of pretreatmentACC activity and lesser reactivity in the amygdala in anticipation of facial presentation were associated with better reductions in anxiety and worry symptoms after 8 weeks' treatment with venlafaxine. This suggests that ACC-amygdala responsivity could prove useful as a predictor of antidepressant treatment response in GAD.[59,60] Interestingly, Pantazatos et al[61] reported that SAD is characterized by reduced functional connectivity in left hippocampus-left temporal pole, and this feature has discriminated SAD from both PD and healthy controls and has increased following the 8 weeks' treatment with paroxetine. This study suggests promise for emerging functional connectivity-based biomarkers for SAD diagnosis and pharmacological treatment effects. In addition, greater right amygdala-pregenual ACC (pgACC) connectivity and greater left amygdala-pgACC coupling encompassing medial prefrontal cortex predicted better symptom improvement after CBT in patients with generalized SAD.[62] This is in good accordance with previous observations that pretreatment cortical hyperactivity to social threat signals can predict CBT success in this disorder.[63,64] The resting-state fMRI study in PTSD patients has revealed that regional spontaneous activity of precuneus and OFC could be a potential prognostic indicator for chronic treatment with antidepressants.[65] In another study PTSD responders to psychotherapy showed increased pretreatment activation of the left inferior parietal lobe during contextual cue processing compared with nonresponders. This activation predicted percentage symptom improvement and therefore could be served as a valuable predictive biomarker for PTSD treatment response.[66] The earlier fMRI studies had demonstrated that poor improvement after a CBT course is associated with greater bilateral amygdala and ventral anterior cingulate activation in response to masked fearful faces, suggesting that excessive fear processing of emotional stimuli may be a key factor in limiting responses to psychotherapy of PTSD.[41] Finally, promising biomarkers for the effects of

SSRIs were recently identified by fMRI approaches in patients with OCD. As was reported, the response to chronic medication with SSRI medications is correlated with changes in connectivity degree in right ventral frontal cortex[67] as well as activation in the right cerebellum and in the left superior temporal gyrus.[68]

Radiotracer brain imaging techniques with SPECT and PET can contribute to further understanding of the biomarkers underlying mechanisms and efficacy of therapeutic intervention.[69] A number of studies have examined changes of regional cerebral blood flow (rCBF), regional glucose metabolism (rCMRGlc) or key proteins of neurochemical systems, including serotonin, dopamine and γ-aminobutyric acid (GABA), in psychiatric patients. However, again, up to now, a very limited number of studies using SPECT or PET have specifically explored the predictive value of the aforementioned functional imaging with regard to the treatment response to antidepressant medication, with the most fruitful findings raised from studies in depression. For example, the treatment response to SSRI antidepressants in depression was strongly predicted by pretreatment binding of serotonin transporters in several mood-related brain regions, including diencephalic structures, bilateral habenula, amygdala-hippocampus complex, and subgenual cingulate cortex[70,71] as well as by rCBF and rCMRglu measures in some other brain regions.[72,73] In addition, Parsey et al[74] have reported that the predictive effect of serotonin 1A receptor binding potential to treatment outcome of antidepressant in depression is modulated by a specific gene variant or polymorphism. As regards the evidence in anxiety disorders, the increase of rCMRGlc was detected in global neocortical areas as well as limbic areas after 12 weeks of escitalopram treatment in PD responders, but not in nonresponders. However, both groups showed pretreatment metabolic reductions which would have unclear predictive value.[75] The different treatment-induced coactivations of rCBF between the left amygdala and the dlPFC as well as the rostral ACC were observed among responders and nonresponders to SSRIs and placebo in large samples of SAD and can be considered as useful neuromarkers, differentiating between successful and unsuccessful anxiolytic treatments.[76] The earlier study with a small sample of patients with SAD has reported that nonresponders to SSRI medication had higher rCBF at baseline in the anterior and lateral part of the left temporal cortex and the lateral part of the left midfrontal regions as compared with responders.[77] Additionally, the magnitude of treatment response to tiagabine, was inversely correlated with pretreatment rCMRglu within vmPFC in patients with generalized SAnD.[78] Recently, the large study in OCD has suggested that baseline increased rCBF in forebrain regions and decreased perfusion in posterior brain regions can be potential predictors of treatment response to monotherapy or combined medication with SSRIs.[79] Furthermore, the higher whole brain perfusion[80] as well as higher rCBF values in posterior cingulate cortex, but lower in OFC[81] have predicted better response to 12 weeks' medication with fluvoxamine in OCD patients, whereas responders, but not nonresponders, showed increased rCBF in the thalamus after treatment, indicating an important role of the thalamic area in drug response.[80] In contrast, no pattern of baseline activation that distinguished responders from nonresponders to subsequent SSRI pharmacotherapy was detected in another SPECT perfusion study, which included SAD, OCD, and PTSD samples.[82] This study is in good accord with the results of Seedat et al[83] who also observed no significant pretreatment differences between PTSD responders and nonresponders in anterior cingulate perfusion, and even deactivation in the left medial temporal cortex following medication with citalopram, irrespective of clinical response. Interestingly, these conflicting pieces of evidence drawn from imaging studies with pharmacological treatment are in line with results from trials that have applied psychological interventions. So no significant differences in pretreatment rCBF were observed between responders and nonresponders to behavior therapy, however the post-treatment rCBF values in the left medial prefrontal cortex and bilateral middle frontal gyri were significantly lower in the responders than in the nonresponders.[84] In addition, no correlation was found between the changes in rCBF and clinical measures in PD patients completed CBT course[85]; however, treatment effects of brief eclectic psychotherapy on PTSD symptoms correlated positively with activation in the left superior temporal gyrus, and superior/middle frontal gyrus.[86]

As regards SPECT and PET studies of neurochemical systems, several research groups have revealed state changes in availability or density of neurotransmitter receptors and transporters in brain of patients with anxiety disorders; however, the predictive value of these changes on antidepressant response has still not been es-

tablished.[87-89] Finally, other neuroimaging methods, like MR spectroscopy, electroencephalography, and magnetoencephalography, showed promising advantage in detection of biomarkers for pharmacoresponse in depression[90-93] and can thus open up new fields in further research of treatment predictors in anxiety disorders.

Genetics

There is a belief that responsiveness to or tolerability of treatment may be influenced by inherited factors. In particular, pharmacogenetic investigations have suggested that differences in antidepressant efficacy can be determined by certain genetic variations inpatients. These studies have multiplied in the past decade due to the improved technology for measuring gene variants with the potential impact that finding reliable genetic predictors might markedly have on everyday clinical practice.[94, 95] However, the best strategy to detect the key markers involved has not been clearly identified, since both candidate gene studies and genome-wide association studies (GWAS) have provided results which fell short of the expectations.[96] To date the majority of candidate-gene studies in the antidepressant field have been conducted in patients with depression and have investigated metabolism-related genes, those that code for receptors and transporters, and those related to second-messenger systems. The most promising results in the pharmacokinetic field have been reported for genetic variations of genes coding for CYP2D6 and P-glycoprotein, although comparative evidence between different drugs is present only for the CYP2D6 gene variants.[97] A complicating factor in relation to drug actions in the brain is that the number of potential pharmacodynamic targets appears to be quite large. The most important of a very long list currently appear to be genes coding for tryptophan hydroxylase, catechol-O-methyltransferase (COMT), monoamine oxidase A (MAOA), serotonin transporter (5-HTT), norepinephrine transporter (NET), dopamine transporter (DAT), monoamine receptors (5-HT1A, 5-HT2A, 5-HT6, 5-HT3A, 5-HT3B, β1 adrenoceptor), dopamine (DA) receptors, G protein β3 subunit, corticotropin-releasing hormone (CRH) receptor I (CRHR1), glucocorticoid receptor, angiotensin-converting enzyme, circadian locomotor output cycles kaput (CLOCK), nitric oxide synthase, interleukin (IL)-1β, and brain-derived neurotrophic factor (BDNF).[98]

Recently, the GWAS approach has been proposed as having a powerful advantage in overcoming the major limitations of candidate gene studies, as they allow us to genotype the hundreds of thousands of polymorphisms across the whole genome, skipping the need for a priori hypothesis and providing novel information about involvement of genetic variation in the phenotype or process of interest. The available GWAS so far, and their meta-analyses, suggest that some single nucleotide polymorphisms (SPNs) including in 5-HT2A, UBE3C, uronyl-2-sulfotransferase and interleukin-11 genes, can be useful markers of treatment response to antidepressant medication in depressive patients.[15] In contrast to the wealth of pharmacogenetic studies in depression, the research of genetic markers of treatment response in anxiety disorders is still limited to single, nonreplicated candidate-gene trials in relatively small samples. So, two available studies in PD have demonstrated that better response to SSRI treatment is predicted by L-form of 5-HTTLPR and the 5-HT1A receptor -1019C/G polymorphism, respectively.[99,100] The LL genotype of *5-HTTLPR* was also associated with greater responsiveness to sertraline treatment and with lower dropouts due to adverse events among PTSD patients.[101] In addition, reduction in social anxiety symptoms during SSRI treatment was significantly associated with *5HTTLPR* genotype in very small samples.[102] However none of three gene candidates, (*5-HTTLPR, COMT* and *TPH2*) predicted the response to CBT in another, larger study.[103] Recently, the most powerful study (in 346 patients) with SAnD has found that two of the four RGS2 SNPs predicted remission to sertraline treatment, what suggests that this gene can be a biomarker of the likelihood of substantially benefiting from SSRI medication among patients with social phobia.[104] An intensive search for genetic predictors has been also conducted in GAD, where a few genes, including the pituitary adenylate cyclase-activating peptide *(PACAP), 5-HTTLPR,* the serotonin 2A receptor gene *(HTR2A)*, corticotropin-releasing hormone receptor 1 *(CRHR1),* dopamine receptor D3 *(DRD3),* nuclear receptor subfamily group C, member 1 *(NR3C1)* and phosphodiesterase 1A *(PDE1A)*, were found as potential markers predicting treatment response to venlafaxine XR or duloxetine medication.[105-111] However, the most intriguing pharmacogenetic findings involving both pharmacokinetic and pharmacodynamic lines of evidence have emerged from studies in OCD and have been reviewed

in more detail in very comprehensive paper by Zai et al.[112] As they summarized, only two CYP450 liver enzyme genes, *CYP2D6* and *CYP2C19*, have been studied in relation to the antidepressant response in OCD. This showed that nonresponders appear to be more common among non-extensive metabolizers according to genetic status of *CYP2D6*, suggesting that genes regulating metabolism of drugs play an important role in treatment response. As regarding the pharmacodynamic studies in OCD, then available data are still inconsistent, preliminary, or not yet replicated in independent, well-powered samples. Among various candidate genes a number of those related to serotonin, glutamate, dopamine systems and neurotrophic factors have been identified as promising genetic predictors of treatment response to antidepressants in OCD.[112] Furthermore, OCD remains the only single anxiety disorder, where the GWAS approach was applied to detect novel biomarkers of treatment response. Many new loci were identified as top hits in the recent GWAS of antidepressant response in OCD patients, including the *GRIN2B, GPC6, DISP1, ANKFN1, ARRDC4, TIAM1, PCDH1D*, *LOCT30101* and *PCDH10* genes; however, a great deal of further research is required to clarify their functional status and their potential role in the treatment response.[112]

Rapid progress in genomic research and bioinformatics promises to provide the technology for far more explorative and powerful approaches in discovery of novel biomarkers, for example via transcriptional and microRNA analyzing. So, microarray studies of peripheral gene transcription signatures have suggested a shared expression of the majority of genes in brain and peripheral blood, and have identified unique gene expression profiles in patients with depression and anxiety disorders, and healthy subjects vulnerable to anxiety challenge tests. In our recent study we used the Illumina microarray platform for whole-genome expression profiling in depressive patients receiving 12 weeks of medication with escitalopram. We found that the magnitude of the expression of some specific genes, *YWHAZ, NR2C2, ZNF641* and *FKBP1A,* responsible for neurotrophin, immune and actin-related processes, differentiated responders and nonresponders to medication and could be used as earlier predictors of treatment outcome.[113] In addition, we conducted the first application of full exome sequencing for the analysis of pharmacogenomics on antidepressant treatment in depressive patients and discovered that the A allele of rs41271330 variation in the bone morphogenetic protein (BMP5) gene is a strong predictor of treatment resistance to escitalopram therapy in depression.[114] Taken together these both methods seem highly promising in further search of treatment biomarkers in anxiety disorders.

Blood-based biomarkers

Plasma appears to be a rational source for proteomic and metabolomic measurements in psychiatric conditions because it is easily accessible, and several molecules from the brain are transported across the blood–brain barrier and reach the circulation. However, the blood-based biomarkers of treatment response in psychiatric disorders remain in very early stages of development and none have demonstrated reliability for predicting pharmacological outcome.[15] This is particularly true for anxiety disorders, where only a few studies have been performed on plasma-based treatment predictors. Due to the strong involvement of stress-related systems in PTSD neurobiology, the neuroendocrine measures of treatment response have been used in PTSD patients and provided some proof of concept.[115] For example, Olff et al[116] found an increase in dehydroepiandrosterone (DHEA) levels among those who responded to treatment for PTSD. Another study found that nonresponders to treatment for PTSD resulting from the 9/11 World Trade Center terrorist attacks had significant declines in post-treatment cortisol levels that distinguished them from responders.[117] The measuring of peripheral serotonergic parameters, like whole-blood serotonin concentration, platelet serotonin transporter, 5-HT2A receptor binding characteristics and platelet IP3 content, is the oldest classical approach, which has identified some predictors of clinical outcome of the treatment in OCD patients medicated with SSRIs. In particular, Delorme et al[118] have reported that higher whole-blood serotonin concentration is predictive of better improvement to 8 weeks' treatment with SSRIs in OCD patients. In addition the β-adrenoceptor affinity (1/Kd) was decreased and adaptively normalized after treatment with paroxetine in the acute panic patients. Also a low pretreatment β-adrenoceptor affinity was found to predict the treatment response to paroxetine in patients with PD, and was suggested as a biomarker of pharmacological outcome in PD.[119] Finally, a lower concentration of serum brain-derived neurotrophic factor (BDNF) was associ-

ated with poor response to CBT in patients with PD, suggesting that BDNF might contribute to therapeutic response in panic disorder. However, further clinical trials with pharmacological intervention are required to confirm this suggestion.[120]

Conclusions

Overall, there is increasing effort to find reliable biomarkers for prediction of treatment outcome in anxiety disorders. However, as with research in disorders close to anxiety disorders such as depression, there are still not any biologic or genetic predictors of sufficient clinical utility to inform the selection of a specific pharmacological compound for an individual patient, because of low sensitivity and specificity of suggested biomarkers.[26] Moreover, the multiple limitations of available studies make the picture of biological predictors of pharmacological response in anxiety far from complete. Most of these studies have been conducted in small samples and had clear shortcomings in their clinical design and treatment outcome assessment. Furthermore, different anxiety disorders are not equally covered by research interest and some particular phenotypes have been almost ignored by investigators to date. All of these limitations significantly complicate our understanding about the role of biomarkers in treatment prediction. Nevertheless, there is strong belief that advanced approaches, including neuroimaging and genetic and proteomic techniques, as well as their combination, should contribute to novel discovery of treatment predictors in anxiety disorders. The one facilitating factor for further research in this area could be previous achievements in depression due to the fact that both conditions, depression and anxiety, are highly comorbid with each other, and both respond well to the same classes of antidepressant medications. So, the existing data obtained by research in depression may stimulate further projects and studies in anxiety disorders. First of all, it will help to validate already known biological predictors of therapeutic outcome to pharmacological intervention, and secondly it will direct us toward the identification of unique biomarkers underlying treatment response in various phenotypes of anxiety. ❑

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Predictores biológicos para la farmacoterapia en los trastornos de ansiedad

Al menos un tercio de los pacientes con trastornos de ansiedad no responden adecuadamente al tratamiento farmacológico disponible. La razón del porqué solo algunos pacientes con trastornos de ansiedad responden bien a la misma clase de fármacos aun no está totalmente aclarada. Se ha sugerido que algunos factores biológicos pueden influir en los mecanismos terapéuticos de la ansiedad y por lo tanto podrían ser identificados como posibles biomarcadores para predecir la respuesta terapéutica. En este artículo se revisa la evidencia actual que explora diferentes tipos de predictores terapéuticos, incluyendo las neuroimágenes, los factores genéticos y las mediciones sanguíneas, los cuales podrían generar nuevas posibilidades en el manejo clínico de los pacientes con trastornos de ansiedad.

Prédicteurs biologiques du traitement pharmacologique dans les troubles anxieux

Au moins un tiers des patients qui ont des troubles anxieux ne répondent pas suffisamment aux traitements pharmacologiques disponibles. Nous ne comprenons pas encore très bien pourquoi certains patients qui ont des troubles anxieux répondent bien, mais d'autres non, à la même classe de médicaments. Plusieurs facteurs biologiques pourraient influer sur les mécanismes de traitement dans l'anxiété et donc être identifiés comme des biomarqueurs éventuels prédisant la réponse au traitement. Dans cet article, nous analysons les données actuelles explorant différents types de prédicteurs du traitement, dont la neuro-imagerie, les facteurs génétiques et les mesures sanguines, qui peuvent ouvrir de nouvelles perspectives dans la prise en charge clinique des patients atteints de troubles anxieux.

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