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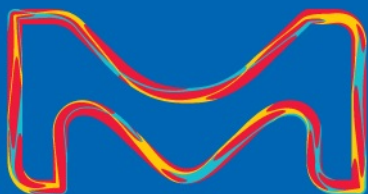
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## REVIEW

DRUG DEVELOPMENT RESEARCH

WILEY

# Biomarkers to predict staging and treatment response in opioid dependence: A narrative review

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## Abstract

Opioid use disorder is a devastating disorder with a high burden in terms of overdose mortality, with an urgent need for more personalized prevention or therapeutic interventions. For this purpose, the description and validation of biological measures of staging or treatment response is a highly active research field. We conducted a narrative review on the pathophysiology of opioid use disorder to propose staging of the disease and search for research studies proposing or demonstrating the predictive value of biomarkers. We propose a IV stage description of opioid use disorder, from (I) vulnerability stage to (II) disease progression, (III) constituted opioid dependence and were several type of treatments can be applied, to the reach a (IV) modified health state. We classified biomarkers studies according to the stage of the disorder they were intended to predict, and to the three categories of methods they used: anatomical and functional aspects of the brain, genetic/transcriptomic/epigenetic studies, and lastly biomarkers of systemic modifications associated with opioid use disorder, especially regarding the immune system. Most studies predicting Stage III that we reviewed collected data from small samples sizes and were cross-sectional association studies comparing opioid dependent patients and control groups. Pharmacogenetic biomarkers are proposed to predict treatment response. Future research should now emphasize prospective studies, replication in independent samples, and predictive value calculation of each biomarker. The most promising results are multimodal evaluations to be able to measure the state of the brain reward system in living individuals.

## KEYWORDS

biomarkers, staging, opioid use disorder

## 1 | INTRODUCTION

Opioid use disorder is a devastating disease for affected subjects, their families and the society (Strang et al., 2020). This disorder constitutes a major health issue in several parts of the world, both in developed and developing countries, and there is an urgent need to increase the research efforts. The North-American continent is markedly affected, especially in terms of overdose-related mortality (Kreek et al., 2019). Various illicit or prescribed opioids have been the first causes of drugs-related deaths in the USA in the past years, namely fentanyl, heroin, hydrocodone, methadone, morphine, oxycodone, in

the 2011–2016 period (Hedegaard et al., 2018). The number of opioid-related deaths has constantly increased in the 20 past years to reach 50,000 deaths per year, for an estimated number of 39 million subjects with heroin or prescription opioid use disorder (Kreek et al., 2019). In Europe, the number of high-risk opioid users is much lower, estimated to be 1.3 million, around 0.5% of the adult population. They cite heroin as the most frequent opioid they consume. Heroin is also the most frequently identified in drug-related deaths in Europe, where it is involved in 82% of the 9000 deaths (European Monitoring Centre for Drugs and Drug Addiction., 2020). This relatively low rate of opioid-related deaths is usually explained by the still

lower prescription rate of opioids (van Amsterdam & van den Brink, 2015) and the higher treatment access to opioid agonist therapies for patients with opioid use disorders. As an illustration the number of subjects receiving opioid maintenance treatment in Europe is estimated to be 660,000, for an estimation of 1.3 million high-risk opioid users (European Monitoring Centre for Drugs and Drug Addiction., 2020), while there are 480,000 subjects receiving an opioid agonist treatment users in the USA for a number of heroin-dependent subjects estimated to be 5.3 million (and up to 37 million if illicit use of prescription opioid is considered) (Kreek et al., 2019).

To face this opioid crisis, governments and scientists have called for action, including an increase in research to identify innovative treatments. In this research plan, identifying biomarkers of treatment response or staging could be a keystone to offer more personalized care or prevention.

## 2 | METHODS

We conducted a narrative review, including original research papers but also literature reviews, on biomarkers of opioid use disorder staging and treatment efficacy prediction. We present the results by starting with a recent update on the pathophysiology of the disorder in order to propose a definition of stages in this disorder. We next reviewed studies that described or/and tested the predictive value of candidate biomarkers of staging and treatment response in opioid use disorder in several domains: anatomic/functional biomarkers of the brain reward circuit changes, genetic/genomic biomarkers, and biomarkers of the immune system/hypothalamic-hypophysial-adrenal axis/oxidative stress that are associated with the disease progression of opioid use disorder.

## 3 | RESULTS

### 3.1 | Staging

Contrarily to most psychiatric disorders, the pathophysiology of opioid use disorder acquisition, evolutive course and treatment is relatively well-known (Strang et al., 2020).

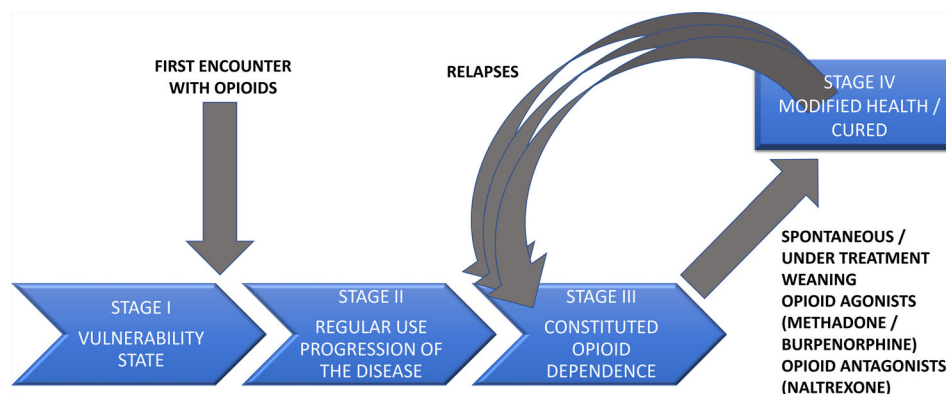
It is now well-established that opioid use disorder is a chronic brain disease, acquired with the repetitive self-administration of opioids. This self-administration progressively shifts the adaptive brain reward circuit, intended to facilitate the identification and selective attention to normal rewarding behaviors into a specialized, rigid, abnormal adaptation to detect, allow selective attention and use a specific drug. This pathological state is accompanied with several other changes in the behavior and subjective feelings of affected subjects, such as withdrawal symptoms when the drug is not taken, or the reduction of other behaviors repertoire.

The mechanism of this homeostatic shift is mediated by the repetitive stimulation with high affinity opioid ligands of the  $\mu$  opioid receptor, whatever the type of opioid used. This receptor stimulation leads to a cascade of intra-cellular second messengers, up to changes in the gene-expression and protein synthesis in the neurons. Opioid receptors are ubiquitous in the brain, but some are located on GABAergic neurons located in the VTA (ventral tegmental area) and inhibits their GABA release on Dopaminergic neurons, leading to an activation of the Dopamine release in the axone, terminating in the NAC (Nucleus accumbens) postsynaptic neurons to activate the reward circuitry. This explains the highly rewarding effect of  $\mu$ -opioids agonists, along with their numerous central and peripheral subjective effects (Strang et al., 2020).

This pathophysiology led us to propose to describe opioid use disorder as a four stages disorder (Figure 1).

The first stage is a stage of vulnerability pre-existing to the first encounter with the drug. The second stage is a stage of disease progression where the homeostatic changes in the brain reward circuit are progressively constituted with the repetitive self-administration of the drug, and a third stage where the disease is constituted. Then, several treatments may be applied, leading to a fourth stage of modified health that can be under opioid prolonged agonist treatment, although relapses are frequent.

An ideal biomarker would be a repeatable biological measure, able with a fair sensitivity and specificity, to detect or predict the stage of disorder where a given subject is or to predict if a given subject would respond to a specific type of treatment. To do so, the perfect biomarker would be reflecting the pathophysiology of the disorder. The perfect biomarker should not only have been observed in a sample of subjects, but ideally its predictive value should have been



**FIGURE 1** Opioid disorder description in four stages of evolution: A chronic and relapsing acquired brain disease, with a marked tendency to relapse even under appropriate treatment



prospectively tested in independent samples of subjects to detect stages change or treatment response.

## 3.2 | Currently studied biomarkers

A summary of the selected articles is given in Table 1.

### 3.2.1 | Stage I: Vulnerability to the disease or high-risk subjects

Epidemiological studies have since many years identified that opioid dependent subjects display a high proportion of vulnerability factors. Those factors include childhood adverse events or trauma history, psychological vulnerabilities such as high sensation seeking or high impulsivity, preexisting psychiatric disorders especially externalizing disorders, and so forth. These results suggest that nonspecific “high-risk mental states” may constitute over time a brain reward circuit that would be more prone to be stimulated by opioid use or highly favor the development of opioid use disorder when the subject encounters the drug. Although those epidemiological findings are also supported by the biological findings observed in subjects with already constituted opioid dependence (Stage III) or even in animal models observing the development from birth to adulthood, there is to date, to the best of our knowledge, no methodologically robust study establishing a biomarker of vulnerability to develop opioid use disorder in Humans. Even genetic studies trying to assess vulnerability with candidate genes approaches or GWASes (genome wide association studies) conducted without a prior hypothesis are only comparing Stage III patients with control subjects, mainly healthy controls, and are finally only able to detect biomarkers of constituted opioid use dependence if any. To date, no genetic polymorphism, alone or in combination in a polygenic risk score, has a predictive power to detect subjects who are at-risk of opioid use disorder before their first opioid use.

### 3.2.2 | Stage II: Disease progression

During the second stage of the disease progression, the homeostatic changes in the brain reward circuit are progressively taking place, and some of them are clinically detectable. We propose to use the clinical category of “abuse” rather than dependence in the former DSM IV classification, or “misuse” in the ICD classification, or DSM 5 opioid use disorder of mild or moderate severity (2 to 5 criteria) to describe this second stage. The clinical signs to detect abuse may include persistent use despite already repeated health or familial or professional damages. Patients may describe a pharmacological tolerance, an attentional bias toward opioids, and already dysphoric states when not using the drugs, most likely reflecting the brain reward circuit modifications associated with this stage. Those modifications could be  $\mu$ -opioid receptors re-arrangements, or second messengers cascade shifts. Nevertheless, establishing the predictive power of biomarkers

of Stage II is methodologically complicated. It would require studies comparing controls or subjects in Stage I to subjects in Stage II and to constituted opioid dependent subjects in Stage III. We could not identify such studies in the literature. This may be due to progressive rather than clear-cut boundaries between stages.

### 3.2.3 | Stage III: Constituted opioid dependence

Once that a given subject is opioid dependent, he/she presents with the clinical characteristics of the disorder: a typical withdrawal syndrome as soon as the drug is not sufficiently present in the organism, a constant urge and a large amount of attention dedicated to identification of the drug itself or the ways to obtain it, the reduction of drive, pleasure from and attention to other usually rewarding behaviors. We propose to use the clinical category of DSM IV or ICD 10 dependence, or DSM 5 opioid use disorder of severe intensity (6 or more criteria out of 11) to describe the Stage III.

Several cross-sectional studies compared subjects suffering from opioid use disorder to control subjects (mostly normal subjects exempt from psychiatric or addictive disorders). In such, they defined candidate biomarkers whose predictive properties were not, for most cases, later tested in independent samples. The methods or tools used in those association studies can be divided in three main categories: biomarkers reflecting the neuroanatomy or function of the brain reward system, genetic/transcriptomic/epigenetic studies identifying characteristics more frequent in subjects with the disorder, biomarkers exploring systemic biological modifications associated with the disease and affecting functions not directly related to the brain reward system, such as immune system/stress response/oxidative stress biomarkers.

#### *Anatomical and functional aspects of the brain*

Of course, biomarkers giving an insight on the current state of the brain reward system would be the more appropriate to predict the disease stage in patients and to serve during the course of treatment as direct therapeutic targets or at least as correlates of treatment efficacy and disease control.

Cross-sectional association studies have established several neuroimaging characteristics of opioid dependent individuals. Among them, we can find altered whole brain cortical thickness (M. Li et al., 2014), and regional gray matter reduction (Liu et al., 2009; Lyoo et al., 2006) compared with healthy controls. This decrease in gray matter density could be correlated with heroin use duration in the prefrontal cortex, insula, anterior cingulate and temporal regions (Yuan et al., 2009; Yuan et al., 2010), and some of those gray matter reduction may be reversible after 1 month of heroin abstinence (Wang et al., 2012). The DTI (diffusion tensor imagery) could be an interesting biomarker because this technique explores white matter integrity, including white matter fibers constituting the bridges between several brain regions, and can describe cortico-subcortical networks known to be modified in other substance use disorders (Hampton et al., 2019). Brain function impairments have also been described in opioid use disorder using mostly default network Resting

**TABLE 1** Summary of the selected articles

<i>Stage I: Vulnerability to the disease or at high-risk subjects</i>		
-		
<i>Stage II: Disease progression</i>		
-		
<i>Stage III: Constituted Opioid Dependence</i>		
CNS biomarkers	Measures	Articles
MRI	-Whole brain cortical thickness	Li et al., 2014
+/- Neuropsychological testing	-Regional gray matter reduction -DTI	Liu et al., 2009; Lyoo et al., 2006; Yuan et al., 2010; Yuan et al., 2009; Wang et al., 2012
PET-scan	-Resting State functional MRI	Hampton et al., 2019
Neurotrophins peripheral measures	BDNF, NGF	Forman et al., 2004; Lin et al., 2012 Angelucci et al., 2007
Genetic/transcriptomic/epigenetic	Measures	Articles
GWAS	Single nucleotide polymorphisms without prior hypothesis	Cox et al., 2020; D. Li et al., 2015; Polimanti et al., 2020; Cheng et al., 2018; Gelernter et al., 2014; Nelson et al., 2016; Zhou et al., 2020
PGRS	Score combining several risk polymorphisms	Polimanti et al., 2020
Transcriptomic	-	
Immune system/stress response/ oxidative stress	Measures	Articles
Cells culture or Human blood cells sampling	-Natural killer (NK) cells activity -T cells response (delayed-type hypersensitivity reactions, cytotoxic T-cell activity, T-cell antigen expression, responses to T-cell mitogens) -B cells activity (antibodies formation) -Mononuclear cells activity (phagocytosis, chemotactic responses, interleukin production, generation of activated oxygen intermediates and arachidonic acid products) -Lymphocyte CD14 rate	Eisenstein & Hilburger, 1998; Yeager et al., 1995;
Cross-sectional plasmatic measures	TNF-alpha, interleukin-1, interleukin-beta levels	Neri et al., 2005
Oxydative stress	-GSH (glutathione) concentration and catalase activity in erythrocytes, -Plasmatic TBARS (thiobarbituric acid reactive substances) - Plasmatic protein carbonyls concentration	Leventelis et al., 2019
<i>Stage IV: modified health or curation of the disease</i>		
CNS biomarkers	Measures	Articles
MRI +/- Neuropsychological testing	-DTI	leong & Yuan, 2017
(1)H MRS +/- Neuropsychological testing	-Prefrontal Cortex activity	Huhn et al., 2019
PET-scan	μ-opioid receptors availability in several brain regions	Greenwald et al., 2007
Genetic/transcriptomic/epigenetic	Measures	Articles
Naltrexone response	OPRM1 polymorphisms	Ragia & Manolopoulos, 2017
Buprenorphine response	CYP polymorphisms	Crist et al., 2013
Methodone response	Individualized dose description with candidate gene hypotheses Individualized dose description with GWAS Individualized dose description genome wide methylation in the PBMc	Mouly et al., 2015; Victorri-Vigneau et al., 2019; Crist, Clarke, & Berrettini, 2018; Eap et al., 2002; Fonseca & Torrens, 2018 Smith et al., 2017 Marie-Claire et al., 2016 Marie-Claire et al., 2017

**TABLE 1** (Continued)

<i>Stage IV: modified health or curation of the disease</i>		
CNS biomarkers	Measures	Articles
	Individualized dose description from candidate genes transcriptome from brain tissues QT length during Methadone treatment	Zerdazi et al., 2019
Relapse or drop out from treatments (whatever the treatment)	Serotonin, dopamine or opioidergic pathways genetic polymorphisms	Crist, Li, et al., 2018; Duan et al., 2020; Crist et al., 2013
Subjective treatment response during opioid agonist treatment	GABAergic pathway genetic polymorphism Monoamine synthesis pathway polymorphisms	Wang et al., 2018 Wang et al., 2018
Immune system/stress response/oxidative stress	Measures	Articles
Prospective cells sampling before–after methadone or buprenorphine maintenance therapy	Mononuclear cells activity (lymphoproliferation and production of IL-2, IFN-gamma, IL-4, and TNF-alpha)	Sacerdote et al., 2008

Abbreviations: (1) H MRS proton magnetic resonance spectroscopy. BDNF, brain derived neurotrophic factor; CNS, central nervous system; DTI, diffusion tensor imagery; GWAS, genome wide association study; MRI, magnetic resonance imagery; NGF, nerve growth factor; PBMC, peripheral blood mononuclear cells; PET, positron emission tomography; PGRS, polygenic risk score.

State functional MRI (Magnetic Resonance Imagery) sometimes coupled with impulsivity or error prediction assessed in various neuropsychological testing (Forman et al., 2004; Lin et al., 2012). Those multimodal assessments, combining a broad or regional brain functional measures associated with a neuropsychological testing that can measure one of the functional impairment associated with the disease are the most promising, although to date not reproduced in independent samples or prospectively tested for their predictive value.

Of note, although there is an abundant literature on the hypodopaminergic state of the brain reward system measured with PET-scan (positron emission tomography) associated with dopaminergic release in the striatum after administration of stimulants (cocaine or amphetamines) with D2-receptor activation measured with radioligands in patients with amphetamines or cocaine dependence, such a literature is rare in opioid use disorder, mainly due to methodological problems (Watson et al., 2014).

Lastly, peripheral and systemic neurotrophins (such as BDNF—brain-derived neurotrophic factor) or NGF (nerve growth factor) rates have been proposed as potential biomarkers of opioid use disorders in some studies (Angelucci et al., 2007). They are easy to assess in the peripheral blood, and could, if they are validated, allow repetitive assessment during a prospective follow up in the same individual. But their significance and relevance to describe the complex changes occurring during the various staging of the disease is not known and no prospective study is available to date.

#### *Genetic/transcriptomic/epigenetic studies*

There are several candidate-gene studies that have been conducted comparing opioid-dependent subjects to normal subjects. Most of them investigated genetic variability in the endogenous opioid system

(polymorphism of the  $\mu$  but also  $\delta$  opioid receptor) and in monoaminergic system (mainly dopaminergic and serotonergic system), but also GABA and glutamate neurotransmission system. This variability is susceptible to confer variability in terms of synthesis, receptor fixation or neurotransmitters disposition. In the last few years, we also identified eight published GWASes conducted to test simultaneous and without a priori hypothesis up to 7 million single nucleotide polymorphisms compared patients with opioid use disorder to control subjects or exposed subjects without the disorder criteria. If some studies could not identify significant differences (Cox et al., 2020), other ones with large sample size and power identified either polymorphisms of unknown pathophysiological significance (Li et al., 2015; Polimanti et al., 2020), polymorphisms in genes controlling neuron growth (Cheng et al., 2018), polymorphisms of calcium and potassium channels (Gelernter et al., 2014), then even more recently confirmed previous knowledge that polymorphisms in glutamate (Nelson et al., 2016) or opioid pathways (Zhou et al., 2020) were associated with opioid dependence. Some of those studies are not plain association studies and have included replication in independent samples, or check of the expression of the suspected proteins in brain samples of affected subjects. But to date, no identified genetic variations has enough effect-size or predictive value to be applied in clinics. This may be the case in the next future by combining several polymorphisms in PGRS (polygenic risk scores) (for an example, see Polimanti et al., 2020), in order to predict the risk of entering Stage III after repetitive opioid use or to match specific prevention or treatment interventions.

Transcriptomic, which is the ensemble of methods analyzing gene expression, including various RNA, miRNA assessment, and methylation of certain parts of the genome (participating in the regulation of gene expression) in a specific tissue at a specific moment, indirectly

favoring or preventing the genes expression, is no likely to provide easily measurable biomarkers in Humans. Establishing the value of transcriptomic biomarkers would require specific brain region samples to measure the associated gene expression associated with Stage III of opioid use disorder. Some selected genes whose expression can be measured both in blood cells and brain regions of interest are currently studied. But for the moment, the tested biomarkers cannot differentiate opioid exposed- from opioid-dependent subjects (Montalvo-Ortiz et al., 2019).

#### *Immune system/stress response/oxidative stress biomarkers*

As other neurological or psychiatric disorders, opioid use disorder has an inflammatory/immunological dimension. Although, it is not clear whether opioid dependent subjects in the Stage III of constituted opioid dependence display those inflammatory differences compared with control subjects because those differences are vulnerability factors or because they accompany the disease progression. They could even constitute a complication of the brain reward system modifications of the opioid use disorder.

Because studying the immune status of the brain is methodologically complicated, those studies range from cell culture models of morphine exposition (Eisenstein & Hilburger, 1998), to peripheral immune response measured in healthy volunteers after morphine exposure (Yeager et al., 1995). We could also identify case-control association studies in opioid-dependent subjects under treatment (Neri et al., 2005), measuring various peripheral biomarkers of the immune response, such as TNF-alpha, interleukin-1, interleukin-beta, lymphocyte CD14 rate, or oxidative stress measured by various measures or enzymatic reactions in erythrocytes or plasma, such as GSH (glutathione), TBARS (thiobarbituric acid reactive substances), protein carbonyls concentration, catalase activity (Leventelis et al., 2019). But several confounding factors have to be taken into account in subjects already in Stage III of opioid use disorder: they have higher rates than the general population regarding viral infections, including HIV or HCV, depressive episodes and other pathological states affecting the immune response. Future studies should identify biomarkers of the brain immune status in relation to the modifications of the brain reward system, and they may come from animal studies or new radioligands targeting glial receptors activation involved in the local inflammation status.

### **3.2.4 | Stage IV: Modified health or curation of the disease**

There are great expectations of patients and families to be able to use biomarkers that would determine that a given subject is cured from opioid use disorder after a long term period of abstinence or adequate treatment such as opioid maintenance medication. This would mean that his/her brain reward system has acquired a new homeostasis, and the subject would not be at risk or relapse in case of re-use of opioid, or could safely taper his/her maintenance treatment and not be at risk of relapse. There is still a debate on

whether this Stage IV is a real healing or only a precarious modified state where efficacious treatment should not be stopped for the patient lifetime.

Predicting Stage IV for patients who are currently under one form or the other of treatment is mainly predicting treatment efficacy or the reverse: predicting relapse.

The same three categories of methods have been applied here: biomarkers reflecting the neuroanatomy or function of the brain reward system, genetic/transcriptomic/epigenetic studies identifying treatment response, biomarkers exploring systemic biological modifications associated with the disease control in terms of immune system/stress response/oxidative stress.

#### *Anatomical and functional aspects of the brain*

Predicting the healing or Stage IV in patients with opioid use disorder could theoretically use several neuroimaging techniques such as PET, (1)H MRS (proton magnetic resonance spectroscopy), and functional MRI. Those techniques could observe functional changes in brain function affecting the brain reward circuit, but also other functions altered during the disease evolution of opioid use disorder. Those functions may be improved by prolonged detoxification alone or by the associated pharmacological or nonpharmacological treatments offered such as cognitive bias modification training, virtual reality, motivational interventions, or even neuromodulatory interventions such as neurofeedback, t-dcs (transcranial direct stimulation) or transcranial magnetic stimulation. A consistent clinical finding for the effectiveness of therapeutic interventions identifies the improvement of executive control networks and the dampening of limbic activation.

Multimodal assessments combining brain imagery, magnetic electroencephalography or measured neuropsychological tests of attentional bias, impulsivity, risk-taking behaviors, or *craving*, or all types of behaviors associated with the modified function of brain reward circuit, have tried to identify patients in Stage IV, most of them under opioid agonist therapies. We are aware of only one prospective study (leong & Yuan, 2017), but most studies were obtained by cross-sectional studies comparing relapsers and nonrelapsers. Several anatomic or functional tools have been proposed to explore the relapse risk. They include MRI-measured brain connectivity, especially between regions of interest for the brain reward system or stress regulation, with white matter DTI assessment.

Another team proposed recently to assess Prefrontal Cortex functional activity with near-infrared spectroscopy measured during a cue-induced craving task, combined with craving scores elevation after the task during a 90-days prospective measurement of opioid use despite methadone treatment. They observed a correlation between their model and relapse. (Huhn et al., 2019). This is the closest model we could identify to a real-life assessment of the brain reward circuit present stage during opioid use disorder treatment.

Few studies included a measure of the availability of  $\mu$ -opioid receptor availability in several brain regions of interest with a radioligand in PET-scan procedures that could be proposed as a biomarker of brain reward circuits modifications during treatment (Greenwald



et al., 2007). But no study followed prospectively patients with this type of procedures for long term studies conducted under treatment.

#### *Genetic/transcriptomic/epigenetic studies*

Because remaining in Stage IV usually requires to be able to receive adequate treatment with adequate dosage for an adequate duration, several clinical factors associated with receiving and being compliant with opioid agonist (mainly methadone and buprenorphine) or with opioid antagonist treatment (naltrexone) have been published. The description of clinical factors associated with stability or treatment response and the ability to successfully taper the treatment with low risk or relapse have been published almost since the beginning of opioid agonist treatments of heroin dependence (for a review see [Ksouda et al., 2013; Moolchan & Hoffman, 1994]).

To that respect, the three most prescribed treatments do not have the same status, and personalized prescription can be rationally chosen according to any given subject genetic susceptibility to be responder or to be affected by side-effects that would impair his/her ability to persist at taking the medication.

Naltrexone, the major opioid antagonist, acts as a specific  $\mu$  opioid antagonist. Its binding to the OPRM1 receptor is affected by a functional single nucleotide polymorphism, whose effect on naloxone efficacy has been widely studied in alcohol use disorder (Ragia & Manolopoulos, 2017), but with little clinical relevance. In opioid use disorder, no study has addressed the predictive value of this functional polymorphism on treatment compliance or efficacy.

Buprenorphine is a  $\mu$  opioid partial agonist. It has demonstrated clinical efficacy in opioid use disorder and does not share with methadone the risk of overdose during treatment initiation. It is the most frequently prescribed opioid maintenance treatment in several countries, such as France, Sweden or Greece and more than 220,000 subjects with opioid use disorder receive buprenorphine-based treatment in Europe (European Monitoring Centre for Drugs and Drug Addiction., 2018). Buprenorphine is subjected to hepatic metabolism involving cytochromes that are described as having a genetically-determined variability (Crist et al., 2013), but clinically the relevance of this variability is not observed. All responders receive dosages in a 10-times dose range.

On the other hand, Methadone, the most anciently prescribed opioid use disorder treatment (Kleber, 2008), is widely affected by variability in the dose required to achieve adequate treatment response, due to a fairly inducible hepatic metabolism but also to several genetic polymorphisms affecting its absorption, blood-brain barrier passage, and hepatic disposition. These complex and interacting phenomena lead to a great importance of associated medical conditions, polypharmacy and individual genetic polymorphisms in the personalized prescription of methadone (for recent examples see (Mouly et al., 2015; Victorri-Vigneau et al., 2019), for a more general review see (Crist, Clarke, & Berrettini, 2018; Eap et al., 2002; Fonseca & Torrens, 2018)). Of note, specific genetic polymorphisms have also been associated with methadone-induced side-effects, such as QT length enlargement measures on ECG (for a recent example see [Zerdazi et al., 2019]). As most genetic vulnerability studies, those results were obtained in cross-

sectional association studies, and none of the subjective genetic biomarkers was validated as predictive of relapse or predictive of the need for higher doses in prospective studies.

There is at least one GWAS assessing simultaneously and without prior hypothesis several millions of single nucleotide polymorphisms to show an association with the need of higher dose during methadone maintenance treatment (Smith et al., 2017). It showed an association with a single nucleotide polymorphism located next to the OPRM1 gene. This association has not been replicated in independent samples yet.

We are aware of only one study assessing genome-wide methylation in the peripheral blood cells as a possible biomarkers of the need of high dose during methadone treatment of opioid use disorder (Marie-Claire et al., 2016), and of a few studies of transcriptome analysis, mainly from brain postmortem tissues from deceased opioid dependent subjects (Marie-Claire et al., 2017). To date, the gene expression differences observed between groups have not been demonstrated to be useful predictive biomarkers of staging or treatment response and may affect genes whose role in the pathophysiology of the disease still need to be explained.

Whatever the type of treatment received, studies assessing genetic variability to relapse or drop out from treatment tested candidate-genes located on the serotonin or dopamine pathways, as they are major hub for impulsivity and general psychopathology (for an example, see Crist, Li, et al., 2018 or Duan et al., 2020) or the opioidergic pathway (Crist et al., 2013). More rarely, some studies assessed the genetic variability on candidate genes of the GABAergic pathway or the monoamine synthesis to address subjective treatment response during opioid agonist treatment (Wang et al., 2018).

Once again, no study did establish the predictive value of the proposed biomarkers in prospective studies in independent samples.

#### *Immune system/stress response/oxidative stress biomarkers*

While most studies assessing the immune system abnormalities in opioid use disorders patients were mostly assessing the Stage III, we are aware of one prospective study suggesting that a minimum of 6 months of methadone or buprenorphine maintenance therapy could restore the immune system measured with plasmatic cytokines levels in heroin dependent patients (Sacerdote et al., 2008). These results suggest that cytokines peripheral levels could be used to monitor treatment response to opioid maintenance treatment and could be tested in independent samples.

## 4 | DISCUSSION

In this narrative literature review, we defined four stages of opioid use disorder and identify that three main categories of candidate biomarkers of staging and treatment response have been proposed in the last few years.

The four stages range from Stage I: vulnerability stage, to Stage II: disease progression, Stage III: constituted opioid dependence and lastly Stage IV: modified health or curation.

To date, the proposed biomarkers are either neuroanatomical or functional biomarkers, sometimes combined with neuropsychological testing measuring brain functions impaired during opioid use disorder; genetic/genomic biomarkers or biomarkers of the immune system as a way to assess the systemic modifications associated with the disease.

Due to the difficulties to recruit these patients and keeping them in a cohort, most studies we reviewed collected data from small samples sizes and were cross-sectional association studies comparing opioid dependent patients and control groups. What we need most to improve the transferability to prevention intervention are biomarkers of “at-risk mental states,” or vulnerability to disease acquisition.

We have now a fair knowledge of genetic biomarkers of the variability in methadone dose needed to reach therapeutic response, or the variability of methadone disposition, but as with the other most prescribed pharmacological treatment, those biomarkers have a small effect size and are not easily transferable to the clinic.

The most promising results are the recent studies on biomarkers of healing, suggesting that we are now close with multimodal evaluations to measure the immediate state of the brain reward system, being close to be able to answer to the frequent question “doctor: am I cured?”. Those suggested biomarkers of Stage IV are not easily repeatable, as they combine neuropsychological testing and brain functional imagery, but no doubt that future progresses in the technology will allow rapid and patient-friendly assessments, maybe using portable devices. If they are replicated in independent samples and have a fair predictive value, those biomarkers will get out of the laboratory and join the clinics to serve as prevention, diagnosis, or prognostic tools.

## 5 | CONCLUSION

Biomarkers of staging and treatment response in opioid use disorder is a very active research field, because of the urgent need to propose personalized prevention and therapeutic interventions. The literature is rapidly evolving, with the use of new technologies. Biomarkers with validated predictive values could be used as surrogate endpoints in therapeutic trials assessing the efficacy of pharmacological or non-pharmacological interventions in opioid use disorder. Having easy to measure biomarkers of staging in opioid use disorder would increase the feasibility of disease modifying research in this devastating disorder.

### CONFLICT OF INTEREST

All authors declare that they do not have conflict of interest regarding this work.

### AUTHOR CONTRIBUTIONS

Florence Vorspan, Frank Bellivier, Vanessa Bloch, and Cynthia Marie-Claire contributed substantially to the literature review and the preparation of the manuscript. Florence Vorspan wrote the first draft of the manuscript, Cynthia Marie-Claire and Vanessa Bloch revised the draft manuscript. All authors contributed to writing the submitted draft and approved the final version of the manuscript.

### DATA AVAILABILITY STATEMENT

Data sharing not applicable - no new data generated

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