Chapter 2
Treatment of Psychiatric Disorders: Time for a Paradigm Change?

This chapter outlines the clinical need for improved diagnostic and therapeutic strategies in the field of psychiatric disorders. There is currently only a medium success rate for psychiatrists in accurate diagnosis of psychiatric patients. In addition, the response rate of patients to current medications is only mediocre once a correct diagnosis has been made. These factors can combine and thus have a negative impact on disease outcome. Furthermore, virtually no novel compounds for treatment of these disorders have entered the market over the last few decades. Instead, most new drugs are merely derivatives of the existing ones. This is due to a lack of good model systems in pharmaceutical company pipelines for the testing and development of novel drugs. As a consequence, many of the major pharmaceutical companies are deserting the field of psychiatry as a potential drug market. This chapter introduces the ideas and anticipated benefits of a shift to more individualized or personalized medicine approaches in the identification and treatment of patients with psychiatric disorders (more detailed information is given in Chap. 12). This shift will involve the use of biomarkers for better classification of patients and for use of a biomarker-related readout to guide the discovery and selection of the most appropriate drugs to give to the patients. This has been exemplified by a review of the oncology field, in which such approaches are revolutionizing patient care and survival. There is no reason to assume that this cannot also work for psychiatry.

What Is the Clinical Need?

There is currently an unmet clinical need for molecular biomarkers in studies of major psychiatric disorders to improve diagnosis and treatment options. Thus far, identification of such biomarkers has not borne fruit, most likely due to the fact that the various disorders are still classified based on long-standing out-dated diagnostic concepts used in psychiatry, and because the various disorders are notoriously heterogeneous in terms of their aetiology and symptoms. Also, the identification of

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biomarkers for a disease that has already been categorized based on clinical symptoms may not be useful in the clinic if such categorisations are indeed inaccurate. Thus, innovative approaches for identification of biomarkers for psychiatric disorders are needed which can be used to classify at-risk patients, such as teenagers with prodromal symptoms for psychosis as well as existing patients who are likely to deteriorate to even more severe states. Many researchers and psychiatrists are now in full support of the idea to deconstruct the traditional diagnoses in favour of more empirical methods, such as classification by use of serum or plasma biomarker panels. This is not intended as a replacement for the old method but as a supplement to be co-administered for increased diagnostic accuracy. This is important since the old ways are working—just not a hundred percent of the time. In other words, there is plenty of room for improvement.

What Is a Biomarker?

Biomarkers are physical characteristics that can be measured and evaluated as an indication of a normal biological process, a disease, response to a drug or toxin, or even the history of a medical condition (Fig. 2.1). To be more precise, the FDA has defined biomarkers as "measurable characteristics that reflect physiological, pharmacological, or disease processes in animals or humans". In medical practice, a valid biomarker could be used to identify a syndrome, a treatment response or a clinical course. For practical purposes a biomarker should be measurable with excellent accuracy and reproducibility, within an acceptable time-frame and at a low cost. Ideally, a biomarker would reflect in some way the underlying nature of the disorder or the biological process affected by a drug treatment.

In psychiatric research, the term biomarker has been used for various kinds of measurements ranging from brain imaging analyses, neuropsychological tests, electrophysiological responses or older methods and techniques such as the skin flush response after chemical provocation. This is based on the idea that "normal" people

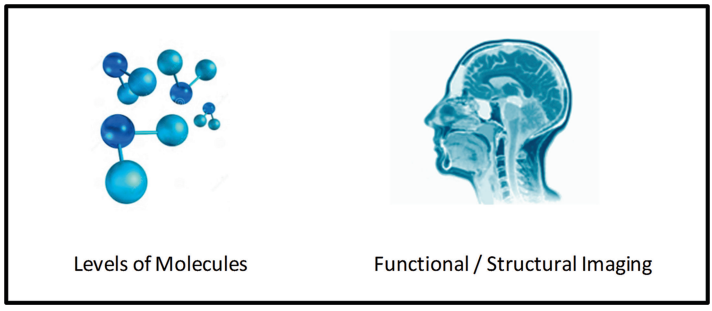

Fig. 2.1 Biomarkers are measured characteristic that can give an indication of physiological status or change

show a skin flush or reddening effect after topical application of niacin to the skin and this may be blunted in patients with schizophrenia. This chapter focuses on the use of molecules identified in peripheral blood (i.e. protein or gene expression data). Furthermore, it focuses on the major psychiatric disorders: schizophrenia, bipolar disorder and major depressive disorder.

Clinical Examples

The following section includes several real life psychiatric case studies for which the clinical outcome could have been improved by incorporation of biomarkers to help with clinical decision making. In all cases the diagnosis of the particular psychiatric condition was uncertain and often changing, and yet treatment was prescribed.

Case 1

A 17-year-old male high school student began to show increased periods of absence from his classes. In addition to this, his test scores were lower than they were previously and he seemed to have problems with attention. It was not long before he was referred to a psychologist. The psychologist diagnosed the student as having an adjustment disorder with an alteration in mood and the possible occurrence of a major depressive episode. The psychologist saw the potential causes for this as relating to the student's uncertainty about future studies as well as conflicts with his father and younger brother. Based on these observations and report histories, the psychologist prescribed treatment with an antidepressant and cognitive behavioural therapy (CBT). In CBT, the therapist tries to help the patient by helping them to choose better strategies for dealing with life's difficulties. At first, the student showed some improvement and he began to attend his classes more regularly, although his overall performance was still lower than before. Six months later, when the student began the final year of his high school, his condition began to deteriorate. During this time he stayed at home and said that he no longer wanted to go to school because he found it to be useless. He also refused to see the psychologist any more for the same reasons.

Naturally, the student's parents had no idea about what to do next. One day, the father made his son get into the car in an attempt to force him to go to his classes. However, the boy ran away and did not return home until several hours later. After this, the boy did not leave his room for several days. The family doctor urged that the student should be admitted into a psychiatric hospital, but the boy refused. A few weeks later, the boy stopped eating because he claimed that the food was poisoned with radio-activity. After this, he underwent forced admission into the psychiatric hospital (this is referred to as involuntary commitment). Over a period of several days, the patient described his beliefs that his school was a centre of evil

scientists who were involved in covering up nuclear accidents and these scientists wanted to kill him because he had discovered this fact. Given this delusion and other factors mentioned above, the boy was diagnosed with schizophrenia. His doctors attempted to treat him with the antipsychotic drugs risperidone and aripiprazole but these led to no improvement. The patient finally improved after receiving treatment with olanzapine, although he still showed some problems in attention and working memory performance. Olanzapine is one of the most wildly prescribed and strongest antipsychotics for treatment of psychosis. Next, his doctors attempted a re-entry programme into the school in which the boy would resume classes the next year, although on a slightly lower attendance level. However, the patient began to show considerable weight-gain over a period of several months to the point of borderline obesity [obesity is defined as having a body mass index (BMI) over 30 kg/m^2]. This is a well known side-effect of olanzapine treatment. Nevertheless, the student did show some improvement of symptoms and the treatment with olanzapine was continued.

What could biomarkers have told us? Well, this case is a classical example on the development of schizophrenia, beginning with symptoms such as atypical mood and motivational changes, as often seen during adolescence. It is not unusual that in the prodromal phases of schizophrenia and other psychiatric illnesses that these symptoms may be attributed to the typical behaviours of adolescence. However, a number of recent scientific studies have now begn to focus on developing a means of identifying young patients who are at-risk for mental disorders such as schizophrenia and distinguishing these from milder disorders, which usually have a more limited time course. These prodromal periods are often referred to as ‘at-risk mental states’, which are usually identified using symptoms that have limited reliability or the presence of certain genetic risk factors. The availability of a biomarker test indicating a likely illness trajectory would have been highly beneficial here. The other factor of this case was that serious metabolic side effects occurred in the form of weight gain, due to a common side effect of antipsychotic treatment. Therefore, a biomarker test which could predict this response may be beneficial as it would allow potential add-on treatments which could potentially combat the weight gain. For example, an anti-diabetic medication could have been used in combination with the antipsychotic. Later chapters describe studies which have attempted to carry this out.

Case 2

A 26-year-old female bank manager was referred to a psychiatrist because she developed several strange ideas including that she was a reincarnation of the prophet. She also said that the future of mankind was threatened and she was insistent that everyone should listen to her warnings. She claimed that she received coded messages from the president of the United States through her television, giving her advice about the fate of the world. She was diagnosed with schizophrenia and her doctors prescribed treatment with the antipsychotic quetiapine. This had some

positive effects through elimination of the delusions and hallucinations but the patient became visibly slower in movement and speech. When she did speak, the only statements she made were those referring to the absence of a future. Following this, her doctor gave a second diagnosis: 'negative symptoms of schizophrenia, possibly depression' and he prescribed an antidepressant in combination with the antipsychotic medication. After 1 week of receiving this new treatment approach the patient showed signs of renewed agitation and restarted her statements about being a prophetess, along with the statements about the end of the world. However, another behaviour began emerge. She began to show signs of sexual disinhibition and even solicited men in bars. She was then admitted to a psychiatric hospital. In the hospital, she wore excessive make-up and talked incessantly. The diagnosis was then changed to mania as part of bipolar disorder or schizoaffective disorder and she was given a mood stabilizer. This treatment had many positive effects and after 3 weeks there was an almost complete recovery.

This case is an example of a patient who has symptoms suggestive of one disorder who then appears to switch to another condition. The reasons for the misdiagnosis are most likely due to the fact that current psychiatric diagnoses are subjective in that they are based on concepts that have both clinical and biological overlaps. However, the availability of a biomarker panel that afforded more accurate diagnosis might have been used to identify the disease correctly. Theoretically, this would allow the patient to be treated with the right drug targeting the right disease for the best possible clinical outcome. This is also in line with the "personalized medicine" concept which is also discussed further in later chapters.

Case 3

A 19-year-old female college student with general good health and no psychiatric history developed auditory and visual hallucinations over a 2-week period. Her general practitioner referred her to a general mental health care facility, where she received an initial diagnosis of psychotic disorder not-otherwise-specified with a possible personality disorder. Based on this, she was prescribed treatment with olanzapine. However, the hallucinations were still present after 1 week and delusions also began to emerge. One of these was the belief that her parents were poisoning her food. She was therefore admitted to a psychiatric hospital, where several clinical diagnoses were considered. These included psychotic disorder not-otherwise-specified, schizophreniform disorder, major depressive disorder and psychotic/mood phenomena with a personality disorder. Routine neurological examinations and laboratory tests were performed but these showed no abnormalities. A gradual amelioration occurred over the next few weeks but the patient showed an inability to concentrate, an altered personality (based on reports of her parents) and mood swings. She was given a psychological test while she was in a state of partial remission which revealed that she had deficits in working memory and sustained attention, and this led her doctors to reach a diagnosis of paranoid

schizophrenia. Following this, the patient developed anxiety and odd movement disorders similar to catatonia (a state of stupor). She was then readmitted into the psychiatric hospital and diagnosed as having had a second psychotic episode. After a few days, she appeared disorientated and had disorganized speech patterns. The results of a brain magnetic resonance imaging (MRI) scan showed no abnormalities although electroencephalogram testing showed signs of encephalopathy, suggesting that the patient may have a brain injury. This led to a new diagnosis of psychosis/schizophrenia with status epilepticus and a possible somatic syndrome. This means that the patient's condition may have resulted from physical symptoms.

Interestingly, laboratory testing showed the presence of antibodies in the serum against the N-methyl-D-aspartate (NMDA) receptor (a type of excitatory glutamate receptor) in the serum and cerebrospinal fluid of the patient. Based on this, a final diagnosis of anti-NMDA receptor encephalitis (a rare disease) was made and the doctors identified a teratoma of the ovary, which was surgically removed. After treatment with anti-inflammatory drugs the patient slowed a slow improvement, although symptoms such as the speech impediments, loss of concentration and altered personality disorder persisted for several months. One year after the final diagnosis, all symptoms had disappeared, and the patient was able to restart her college education.

This case described a patient with a syndrome in which encephalitis is caused by an auto-immune response against an important neurotransmitter receptor. Although this form of encephalitis is considered to be a neurological condition, the clinical presentation can begin with psychiatric symptoms such as anxiety and hallucinations. The lesson here is that biomarker analyses using serological testing for this antibody could have picked up this condition from the start. This would have helped to minimize the duration of illness and reduced the time to recovery.

Case 4

A 68-year-old male admitted to emergency with acute seizures and right hemiparesis, associated with hypoglycaemia. He was referred for a psychiatric evaluation since he had been refusing food and this was thought to be the primary cause of the symptoms. For the previous 8 months, he had been presenting with the delusion that he had neck cancer obstructing his throat with clogged even though these had been ruled out by clinical examination. This delusion led to constant food avoidance and fasting and he had frequent episodes of hypoglycaemia. His psychiatric history included only one episode of depression which had been treated successfully 8 years before, although he displayed behavioural changes over the last 2 years which included hiding food and refusing meals. This was associated with physical effects including sweating, slurred speech and tremulousness which were all relieved by forced eating. He also displayed the clinical manifestations associated with some psychiatric conditions, like self-neglect, lethargy, isolation, confusion, disorganized speech, unresponsiveness and poor performance of normal daily tasks. Because of

this, he was admitted to the acute psychiatric ward with a diagnosis of depressive episode with hypochondriac features. He was then treated with the antidepressant venlafaxine and the antipsychotics risperidone and alprazolam. This led to improvements in the eating behaviour problems as well as certain psychiatric symptom scores [Brief Psychiatric Rating Scale (BPRS) and Hamilton Rating Scale for Depression (HAM-D)]. However, hypoglycaemia still occurred even with the normalized feeding behaviour. For this reason, further clinical tests were performed which showed that the patient had very high circulating levels of insulin associated with the low glucose levels. Subsequently, the patient underwent an abdominal computerized tomography (CAT) and transendoscopic ultrasound scans and a tumour was identified and removed. Histopathological testing confirmed this to be an insulinoma. When tested 6 months later, the patient showed no hypoglycaemia and improved psychiatric symptom scores, associated with improved personal and social functioning. Since the patient stilled showed some mild depressive symptoms, the antidepressant was prescribed for 1 more year.

This is another illustration of a case of a suspected psychiatric condition which was actually caused by a somatic condition—in this case the culprit was a tumour called an insulinoma. These tumours produce high levels of insulin, the main hormone responsible for reducing blood sugar levels. Since glucose is a major energy fuel source for virtually all cells in the body (including the neuronal cells in the brain), it is not surprising that the brain would be operating in an energy deprived state and cause the psychiatric symptoms. Again, the lesson to be learned here is that biomarker analyses using blood testing for insulin and glucose would have led to further testing, such as the scans performed above, followed by surgery, which would have helped to minimize the duration of this illness.

The most important point to keep in mind here is that an early and accurate diagnosis can lead to better outcome for the patients (Fig. 2.2).

Current Diagnostic Practices in Psychiatry

Today, rational medicine requires the existence of a valid method to group or classify similar patients using a diagnostic system. This is basically so the right form of treatment can be prescribed for the best possible patient response and outcome. At present, the major psychiatric diagnostic system used in Europe is the Diagnostic and Statistical Manual (DSM) system, with the 2013 DSM-5 as the most recent edition (the method used more commonly in the USA, the International Classification of Diseases Version 10, is discussed later). Even though the influential DSM-III was introduced in 1980, the fundamental concepts of the DSM approach date back to the late nineteenth and early twentieth centuries, when Kraepelin made his observations on the difference between dementia praecox and mania (see previous chapter). Dementia praecox eventually developed as the schizophrenia concept, whereas mania formed the basis for the broad group of mood disorders, which include major depressive disorder and bipolar disorder.

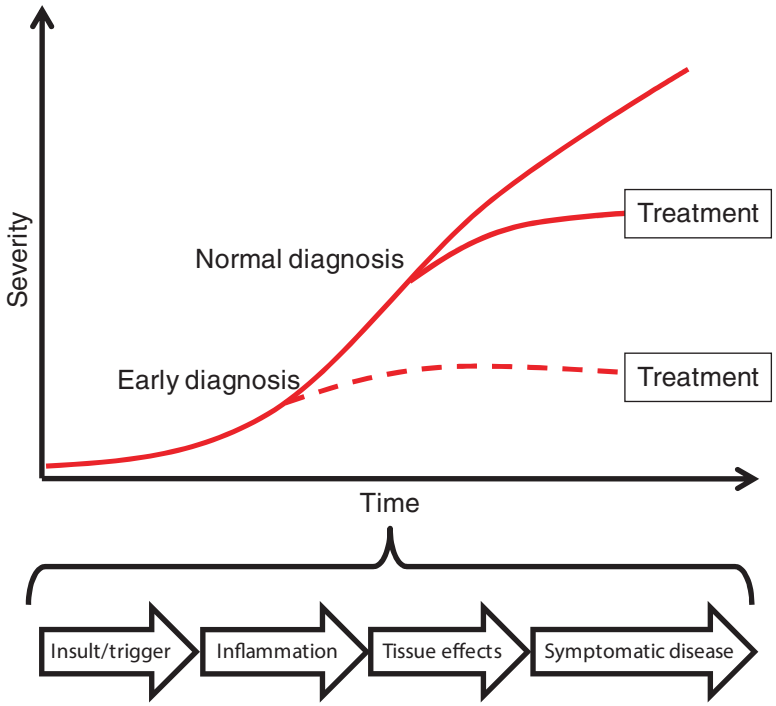

Fig. 2.2 Time-based diagram showing that early diagnosis combined with effective treatment can lead to better outcome for the patients

Most researchers and clinicians are now aware of the fact that the DSM system does not take into account the underlying biological causes of the disorders described in the various diagnostic categories. Instead, it defines these categories using cut-off criteria based on the presence or absence of symptoms. Therefore, these categories within the psychiatric disorders are distinct from other major medical diagnostic concepts, which are mostly associated with underlying biological alterations. Nevertheless, the DSM concepts are not arbitrary and have been chosen based on their clinical validity over approximately 100 years of psychiatric thinking and practice. Indeed, the field of psychiatric research as it is today would not exist without this rigorous system.

It is clear that diagnosis is the principal rate-limiting step in psychiatry and associated research and if clinicians use less than ideal diagnostic categories, the results of these studies will either be absent or clouded by over or under inclusion of patients or controls. Therefore, some or all results derived from such studies might be misleading. The main disadvantage of the DSM diagnostic categories is that they are arbitrary and do not necessarily represent a true medical diagnosis. However, adequate training of clinicians, especially in the use of standardized interviews, can lead to acceptable inter-rater validity using the DSM criteria. Nevertheless, the

validity of DSM constructs is limited with respect to providing information on the affected biological pathways as well as delimitation from other disorders. This is because the DSM categories are heterogeneous as they incorporate many combinations of symptoms arranged into each category. For example, schizophrenia can be comprised of 23 different combinations of symptoms and other observations. Another likely problem is that some researchers argue that there is a continuum between the core psychiatric symptoms, syndromes and normal functioning with no actual discrete boundaries. For example, the distinction between sorrow and depression is not clear.

As an example, recent findings show evidence for overlap between schizophrenia and bipolar disorder. Although DSM makes a distinction between schizophrenia and bipolar disorder, Kraepelin's later work pointed to the similarities in the course of both disorders. Furthermore, there is now evidence that autism spectrum disorders and schizophrenia both show brain connectivity deficits and similar genetic variations making these difficult to distinguish in some cases, especially if the subject is an adolescent. Such findings help us to understand that most psychiatric patients do not meet the criteria of one particular disorder as currently defined but instead they can show signs and symptoms of several of these diseases. Figure 2.3 shows this dilemma in a schematic bubble diagram.

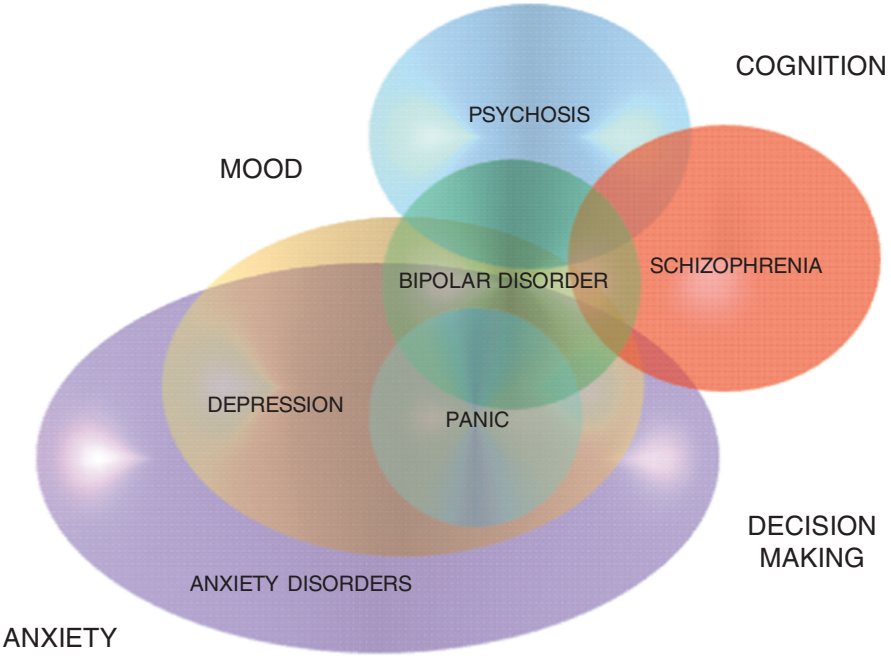

Fig. 2.3 Overlap of psychiatric disorders with respect to effects on various brain functions

How Might Biomarkers Be Used in Psychiatry?

As an Aid to Diagnosis

A logical first step in biomarker discovery would be to investigate an association between biomarkers and a specific diagnostic category. This would require identifying biomarkers which can separate one DSM diagnostic category from another as well as separating patients from so-called "*healthy" control subjects*. However, there are many roadblocks in the way of attempting such an approach. As outlined in the section above, the DSM categories are arbitrary to a certain extent and most likely do not reflect an underlying pathology or biological pathway. This problem is compounded by the fact that most biomarker studies in psychiatry result in considerable overlap across the groups being compared. In other words, they do not tend to make a good distinction across the groups. It would be a breakthrough if a biomarker or set of biomarkers were shown to be specifically related to one or more of the DSM diagnostic categories. However, this would be trivial from a clinical diagnostic point of view, as the category would already be defined by the DSM criteria.

Identification of Diagnostic Subgroups

Another approach is to attempt to bypass the heterogeneity in the DSM categories by going back to the basics of the system. This assumes that there are a limited set of fundamental psychiatric syndromes which can be identified by specific core symptoms. Examples would be: schizophrenia with severe negative symptoms, bipolar disorder in the mania state (more on this later), severe depression with autonomic dysregulation (formerly called endogenous depression) and classical autism. These syndromes are rare but easy to identify due to their severe nature. The first step would be to identify biomarkers that are associated with these syndromes. The next step would be to use these for testing a large group of patients presenting with less specific psychiatric symptoms and attempt to classify these individuals according to their similarities with the fundamental biomarker patterns. The final step would be to investigate whether or not the tested patients with these biomarker profiles have a prognosis or treatment response similar to those of individuals with the associated fundamental syndrome. This would be useful for prescribing the right medications.

Treatment Response Prediction

Biomarkers could also be used for prediction of response of the patients following treatment with specific psychiatric medications. The main goals of this would be to either predict efficacy (effectiveness of treatment) or whether or not the patient

would develop adverse events (side effects), or both. Thus, patients could be divided into subgroups of likely responders and non-responders and at risk or not at risk of developing side effects, respectively. The evidence would be used for making decisions on the medications that patients should receive. Examples of biomarkers which could be used for this could include those derived from imaging techniques, serum assays, genetic profiling, physiological measures, histopathological findings or psychological tests.

There are already some examples of genomic biomarker tests that predict response of patients receiving a drug based on how quickly that drug is metabolized within the patients' bodies. Drugs are normally metabolized as they pass via the circulation through the liver by a family of enzymes called the cytochrome P (CYP)-450s. For example, the selective norepinephrine reuptake inhibitor atomoxetine, approved for treatment of ADHD, is cleared from the body through metabolism by CYP2D6. Therefore subjects who have naturally low levels or poor activity of this enzyme tend to have higher plasma levels of atomoxetine compared to those with normal CYP2D6 activity levels as atomoxetine would not be metabolically cleared as quickly in these individuals.

There are other examples of biomarkers that predict differences in responses based on whether excessive levels of a specific gene or protein are present. For example, the *HER2* gene encodes a cell surface receptor protein that causes growth of breast cancer cells and this gene is over-expressed in approximately one fifth of the women who have breast cancers. This is one of the best examples of personalized medicine in clinical practice today. Patients who have over-expressed *HER2* can be given an antibody with the trade name Herceptin® which binds to and neutralizes the HER2 protein and therefore blocks cancer cell growth. There are also a few examples of personalized medicine in psychiatry. Studies have suggested that patients with a particular nucleotide sequence change (this is called a polymorphism) in the serotonin 2A receptor gene (*HTR2A*) tend to have a positive response after treatment with the selective serotonin reuptake inhibitor (SSRI) citalopram. Although these findings are not as striking as those used in cancer, they give encouragement that searching for biomarkers of psychiatric drug response may be fruitful.

Helping to Redefine the Diagnostic Categories

Previously, I have stated that DSM criteria have limited value in helping to understand the underlying biology of these diseases and should therefore not be used to guide biomarker-based research. So, based on this, one approach of increasing our fundamental awareness of the pathways affected in these disorders would be to abandon the DSM categories altogether, using instead the broad array of symptoms and other factors associated with these diseases. Patients could instead be arranged into broad problem groups that are different from one another in terms of disease course, outcome and presumably the aetiology (the cause of the disease). The next step would be to test this problem group based approach in a mixed group of patients

to determine if these patients could be segregated into distinct groups based on biomarkers. The mixed group could be comprised of current DSM diagnoses including psychotic disorders, bipolar disorder, depressive disorder and various personality disorders. In this way, patients belonging to the same biomarker group will have the same biological profile (at least for those biomarkers investigated) and may exhibit the specific signs and symptoms of a traditional diagnostic category. However, it is more likely that these clusters will consist of mixture of patients exhibiting signs and symptoms of a variety of DSM-defined disorders. Another aspect which could be tested is whether or not the patients of a particular biomarker group have any common clinical characteristics, such as similar prognoses or responses to treatment. An initial form of this approach has been advocated by Van Praag, who defined some basic symptom groups.

Obviously, there are a number of assumptions associated with this approach. The most important of these is that circulating biomarker differences occur and that these differences reflect underlying changes that are common in a particular subgroup of patients. In support of this possibility, one recent study found that acutely ill schizophrenia patients could be classified into two groups which differed in their serum biomarker profiles compared to the profiles in normal control subjects. One group had more alterations in the levels of circulating hormones and growth factors like prolactin, testosterone and insulin, and the other group had changes mainly in immune or inflammatory factors, such as the interleukins 1RA, 8, 16 and 18. This finding may be important as other reports have suggested that some but not all first onset schizophrenia patients have changes in insulin and other molecules related to insulin action. Likewise, other studies have found that approximately half of schizophrenia patients have changes in molecules associated with the inflammatory response.

Helping to Identify Staging of Psychiatric Diseases

Recent years have focussed more on the dynamic nature of psychiatric diseases as occurs in other disorders. One example of this is the different stages of malignancies in various types of cancer. This is especially true if the origins of a particular psychiatric disorder are neurodevelopmental, since this implies an illness trajectory. For example, four stages of schizophrenia have been hypothesized and these are: (1) risk; (2) prodromal symptoms; (3) psychosis; and (4) chronic disability. Risk is the stage before detectable deficits occur and the prodromal phase of schizophrenia is now known to be a valid second stage which occurs before the onset of full blown psychosis. The prodrome stage is identified based on the presence of symptoms such as disturbed thoughts, social isolation and impaired functioning. Some of these features are common during adolescence and the problem of distinguishing a high risk for psychosis from more common adolescent angst has always been a major challenge. At present, diagnosis of schizophrenia is mainly based on the symptoms and signs of psychosis. However, this is likely to occur not at the beginning but

during the course of illness, after a time when some neuronal changes may have already occurred. Chronic disability is the stage of suffering and associated difficulties in patients who have had the disease for several years. The incorporation of biomarker and new cognitive tests, as well as the identification of subtle clinical features, may enable the detection at the earlier stages of risk, such as in the prodrome stage, as well as identification of specific illness trajectories.

What Kinds of Biomarkers Have Been Identified?

Over the last decade, converging results from *post-mortem* research, neuroimaging, genetic association studies and measurements of peripheral blood biomarkers have suggested the presence of several biological themes within the broad context of the schizophrenia syndrome and other psychiatric diseases such as major depressive disorder and bipolar disorder. One of the most recurring themes has been the identification of biomarkers associated with altered glucose metabolism and insulin signalling, growth factor pathways and immunological alterations. In the case of schizophrenia there is also abundant evidence for alterations in dopaminergic- and glutamatergic receptor signalling pathways. In depression these alterations are less clear, but there is long-standing evidence for aberrant HPA-axis signalling (more on this later).

Decreased circulating levels of a protein called brain-derived neurotrophic factor (BDNF) have been identified repeatedly in schizophrenia. Interestingly, this may be dependent on the clinical phase of the disorder as the levels of this growth factor appear to be decreased during acute psychosis and restored to normal levels after remission. Increased levels of inflammation–related molecules, such as interleukin 1, interleukin 6 and tumour necrosis factor, have also been found. But none of this is new. The suggestion of impairments in energy metabolism in psychiatric disorders such as schizophrenia was published almost 100 years ago. Because most of these studies involved taking samples from patients following treatment, hypotheses have emerged and are now established that antipsychotic drugs had a negative impact on glucose metabolism and the insulin response. These days it is well known that antipsychotic drugs such as clozapine and olanzapine can lead to increased body weight, diabetes and hyperlipidemia when given to patients. However, studies over the last 10 years have shown that schizophrenia patients can have insulin resistance, independent of antipsychotic treatment.

In major depression, there have also been numerous reports of alterations in the HPA axis and other hormonal signalling pathways. Evidence for hyperactivity of the HPA-axis was shown by higher levels of the stress hormones CRF, ACTH and cortisol. Also in major depression, convincing evidence of inflammation has been found with increased levels of interleukin 1 and interleukin 6. More details on these biomarker findings are presented in chapters on the major psychiatric disorders schizophrenia, major depression, bipolar disorder, anxiety disorders and autism

spectrum disorders, as well as the neurodegenerative disorders Alzheimer's disease and Parkinson's disease. All of these chapters illustrate how we can study these "brain" disorders by investigating the blood.

Future Prospects

This chapter describes the clinical utility of biomarkers for major psychiatric disorders such as schizophrenia, major depressive disorder and bipolar disorder with a focus on the use of a blood test to improve diagnosis and patient outcomes. At present, there are a limited number of clinically valid biomarkers available for this purpose. This may be due to the fact that these are still linked to old diagnostic concepts which have been in use for decades to classify these diseases. It is likely that efforts along these lines will be challenging, due to the heterogeneity inherent in these categories. Moreover, identifying a biomarker for a syndrome that has already been identified based on clinical phenomenology is not useful from the clinical point of view. We need to go beyond this. Innovative approaches are needed such as identification of biomarkers that can be measured in at-risk individuals with prodromal symptoms. It is hoped that tests can be constructed from such biomarkers and that these can be used to assess possible development of the patients towards more severe states, and thus indicate the optimal intervention for that stage. This approach is aimed at disease-profiling and clinical staging and would therefore be based more on readily observable clinical characteristics. Next, it would be important to use broader categories of related patients, and to deconstruct the traditional diagnoses of these patients using molecular biomarker profiles in addition to, or in place of, the symptom based approach used today. Finally, another use of biomarker tests would be for predicting an optimal treatment response, an approach which has already found some success in cancer studies.

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