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Psychotic Disorders
An Update

Edited by Federico Durbano

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http://dx.doi.org/10.5772/intechopen.70973
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First published in London, United Kingdom, 2018 by IntechOpen
eBook (PDF) Published by IntechOpen, 2019
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, The Shard, 25th floor, 32 London Bridge Street
London, SE19SG – United Kingdom
Printed in Croatia

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Additional hard and PDF copies can be obtained from orders@intechopen.com

Psychotic Disorders - An Update
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p. cm.

Print ISBN 978-1-78923-324-7

Online ISBN 978-1-78923-325-4

eBook (PDF) ISBN 978-1-83881-500-4

Meet the editor

Dr. Federico Durbano was born in Genoa, Italy, in 1963, and he is living near Milan, where he received a degree in Medicine and specialized in Psychiatry. He had different work experiences in some hospitals (Milan "Ospedale Maggiore Policlinico", Treviglio, Melegnano, Fatebenefratelli), where he has achieved significant career milestones, and now he is the Director of the Psychiatric Unit in Melzo Hospital, ASST Melegnano e della Martesana and the Vice Director of the Department of Mental Health and Substance Dependence in the same ASST. He had been teaching assignments at the University of Milan (Nursing School) and University of Castellanza and Business School of Il Sole 24 Ore (Masters in Criminology). Dr. Durbano also attended more than 70 local and national congresses and courses as invited speaker. He published more than 160 papers in national and international journals and books. He also works as a technical adviser to the court in the field of forensic psychiatry.

Contents

Preface

The presented volume has a heterogeneity of topics only at first glance, namely regarding the editorial choice to treat different "psychosis" in the same volume. This decision is a consequence of the rapid development of neurosciences, which are showing common underling factors to different phenotypical expressions of mental illness, but also of some unspecificity in treatment approach. In this book, thanking the contributions of not only the clinical psychiatrists but also of neurobiologists, specific issues of psychotic disorders (mainly schizophrenia and mood disorders) are then reviewed.

A very brief introductory chapter, "Unmet Needs and Future Developments", will introduce the ongoing problems and the unmet needs in managing psychotic disorders.

The awareness of an urgent need for an evidence-based "personalized" but also "human" approach of treatment is growing in the field of psychiatry. In this respect, the first chapter, "The Harrowing", will introduce us to the deep personal experience of psychotic breakdown. The chapter is of great value, since it is not only an internal testimony of psychosis, very well written, but it also stresses the importance of a trustful relationship between the patient and his caregiver.

Following that, but profoundly related to it, the issue of insight is a main outcome factor. The chapter "Lack of Insight in Bipolar Disorder: The Impact on Treatment Adherence, Adverse Clinical Outcomes and Quality of Life" is a fine review of this concept and it describes the potentially negative outcomes of a "bad" insight into bipolar disorder (but the same observations can be generalized to schizophrenia as well).

Another factor having a negative impact on clinical outcome is the one related to negative symptoms. The presented chapter "Negative Symptoms of Schizophrenia: Constructs, Burden and Management" updates the complex construct of negative symptoms, their consequences on intensity of care and some suggestions on their management.

The chapter "Interdisciplinary Rehabilitation to Facilitate Recovery of People Living with Long-Term Schizophrenia in Developing Countries" depicts the objective difficulties in using the more and more growing psychosocial options in countries where the availability of resources is not so high as in wealthy countries. In this context, a reorganization of available resources applied to a more rational choice of therapeutic options is necessary.

The preceding chapter shows how human resources can influence the availability and the use of therapeutic options. In the following chapter, "Genetics and Epigenetics of Schizophrenia", we see how environment can influence the expression of genes in the development from a biologic risk condition to manifest illness.

The importance of immune system as a common pathway in psychiatric illness and comorbidities is increasingly recognized and in the following chapter, "Immune System Dysregulation and Autoimmunity in Schizophrenia: IgGs from Sera of Patients with Several Catalytic Activities", the relevance of this hinge system between internal environment and external one is underlined.

In the last chapter, "Epigenetic and Schizophrenia", the authors have a more molecularly based approach to epigenetics of schizophrenia. Their objective is to give an up-to-date picture of epigenetic data in order to integrate the huge mass of data available.

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Chapter 1

Introductory Chapter: Unmet Needs and Future Developments

Federico Durbano

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.77325

1. Different society = different psychopathology?

Major mental illnesses have modified according to time and space—different historical moments and different countries/cultures (modifications either in prevalence or in form), and as such they are sparked and shaped by the ethos of particular times and places. As enlighted by Shorter in one of his works, every culture possesses a "symptom repertoire"—a range of symptoms (either pure psychological or mixed physical) shaped by the cultural dominant model [1]. Culture shapes the way general psychopathology is going to be translated partially or completely into specific psychopathology. The problem becomes especially worrisome in a time of globalization and world web communications, when symptom repertoires can cross borders with ease and can be absorbed and integrated by different cultures. Our dominant western cultural influence on mental health and illness representation can shape, with a high level of probability, the expression of illnesses in other cultures but the issue is rarely discussed in the professional literature. Despite this, we cannot eliminate the individual suffering of psychopathology: whatever is the name of the illness, a psychotic experience for the individual is devastating and it has profound pitfalls on society and family. But in the meantime, a solely psychopathological (anthropological, sociological, and phenomenological) approach is a limit not in understanding the sufferance but in understanding the underlying mechanisms of the illness. The rapid development of neurosciences will open us a new world in terms of biological mechanisms, of possible specific targets of interventions, a more individualized and specific therapeutic intervention (as it is happening with oncology).

Nevertheless, in the same time, the human ambient (culture, living spaces, human organization) showed a powerful shaping power on illness manifestation and possible treatment (in terms of resources—formal and informal ones). Three large international studies carried out by the World Health Organization since early 1970s showed that schizophrenia has better

prognosis in developing countries than in the developed world (International Pilot Study of Schizophrenia (IPSS), Determinants of Outcome of Severe Mental Diseases (DOSMeD), and International Study of Schizophrenia (ISoS)) ([2], for a synthesis). The researches showed that despite a lack of health resources, patients outside the wealth world (United States and Europe) had as much as two-thirds lowering of relapse rate. These apparent incongruities have put in relation with the way we talk about mental illness, since symptoms are (differently from more "medical" illnesses) deeply influenced by a person's complex interactions with those around him or her. This is what we call also "high expressed emotion" ([3], for a critical review). Some other interpretations underline the role of such factors as the individualistic and internalizing trend of industrial and postindustrial society, with the loosing of social support and of the traditional family environment, the most stressing nature of work, the development of stigma in the more medicalized societies, and the differential survival rates of vulnerable individuals [4]. The role of stigma in postindustrial societies is well described by Watters and by McGruder [3, 5].

2. The role of biology

In this complex systemic organization (biology, culture, and ecological living space), only the understanding of neural, and before them biological at all, mechanisms will be of value in developing more efficient and efficacious treatments, pharmacological but also psychosocial. Interpreting mental illness solely from a neurobiological perspective is by sure dehumanizating, not recognizing the individual experiences and development, but an exclusive sociological reading of mental illnesses will conduce to confusion and a potentially dangerous negationistic position [6–7].

An interesting point of view on the enormous growth of neurobiological data is that expressed by Prof. Maj, a prominent Italian psychiatrist former President of Italian Psychiatric Association: "The huge mass of 'data' or 'evidence' which is being accumulated in this area is not perceived anymore as an indication of a continuing increase of 'knowledge.' Rather, this mass of data is increasingly seen as a sign of uncertainty and confusion." [8].

Taking into account the caveats of Maj, but also underlining the importance of ambient and of individual differences, a modern view of the biological basis of mental illnesses is the epigenetic approach [9–11]. Epigenetic poses that over the biologically "hardware" of genome, there is a sort of "interactive software" between genes and environment where environment has a main role in determining genetic expressivity. This approach can be of help in understanding old concepts like vulnerability, resilience, protective factors, stress reactions, and so on [12].

Afore general observations are needed to understand the only apparent heterogeneity of topics covered by the present volume. First of all, the choice to treat in the same volume different "psychosis". The editorial decision is the consequence of the rapid development of neurosciences, which are unraveling common factors underling different phenotypical expressions of mental illness, but also the substantial unspecificity in treatment approach. In this book,

thanking the contributes not only of clinical psychiatrist but also of neurobiologists, specific issues of psychotic disorders (mainly schizophrenia and mood disorders) are then reviewed according to the general considerations already described.

3. Do not forget persons

A particular topic is the need to develop (or, better, rediscover) an awareness of an urgent need for an evidence-based "personalized" but also "human" approach of treatment. In this respect, the contribute of Susan Weiner is of central impact in introducing us in the deep personal experience of psychotic breakdown. It is an inside witnessing of psychosis, very well written, but also it stresses the importance of a trustful relationship between patient and his caregiver in order to reach a clinically significant result.

Other topics are then developed, ranging from the concept of insight and adherence to the influence negative symptoms have in the clinical management, to the peculiar management of bipolar depression. Other topics of interest are related more specifically to biological basis of psychosis.

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Section 1

A Patient's Perspective on Psychotic Experience and Treatment

Chapter 2

Descent into Darkness

Susan Weiner

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72602

Abstract

This personal narrative of a time with schizophrenia will cover one patient's descent into madness and ultimate recovery from a period that felt like a sentence in a prison of hell and irrationality. Following a breakdown that led to the patient's withdrawal from graduate school, this narrative covers the experience of madness that led to delusions and hallucinations which tyrannized the patient's world. The narrative not only follows the breakdown of humanity that cursed the patient's understanding but also provides for the highlights of recovery that brought about a return to intellectual activities and a full comprehension of experience in the world. Though this patient's life was destroyed by schizophrenia, including the loss of all worldly goods and a career in academia, her experience of caring psychiatrists and a loving family redeemed her life and brought about solace and renewal at last.

Keywords: schizophrenia, madness, delusions, hallucinations, recovery, sanity

1. Introduction

The scientific basis of benefits in autobiographical recall in psychosis is suggested in some recent research and review papers [1–3]. It may also be noted that some books on autobiographical issues in psychosis indicate how important personal memories are in self-help and in explaining the subjective sense of the illness [4–6]. To this end, I offer a narrative of my time in insanity. I hope that it may be illustrative of one person's experience with schizophrenia and thus useful to psychiatrists and others who study not only the neurological changes in the brain but also the subjective experience of an altered reality and its consequences on outlook and behavior.

2. Heading

In the spring of 1993, I came down with schizoaffective disorder. At the time, I was a graduate student in history at a West Coast University in the United States. This disorder took me by the neck, shook out my life and utterly destroyed my career along with my hopes and dreams. To be honest, it shook up my humanity most of all and reduced me to what I now feel was a state of less than an animal. I would say I felt like a cornered beast, alienated from my friends and family and wholly cut off from the human race.

I interacted solely with dreams and created a whole world of delusions that determined how I spent my time and what I understood of reality, such as it presented itself to me. Because I had money to pay for my next year of graduate study, I was able to live off the proceeds and disappear into a large city leaving the real world and my relationships behind as I struggled to understand what I felt was the real truth of the world revealed to me at last.

What I remember most of my time alone with psychosis was how harrowing it was. I lived my days in what I considered a war zone, terrorized by an enemy I believed to be an Adolf Hitler or Saddam Hussein of dictators bent on world domination. In my opinion, I was a spy, modeled on the French Resistance. I thought I was working with a shadowy organization to undermine the growing influence and power of a madman who would surely destroy the world.

In this capacity, fear was my constant companion, my warm blanket in a dark forest of the unknown, helping to manage my response against the biting cold of evil. I regarded it as a necessary implement, useful as wool against a blizzard of pure, unadulterated madness that consumed my days. Though I was insane, I believed I was only now in possession of the real truth of the world. You could not have argued me out of my beliefs. I would have considered you pernicious and in league with the devil. In some ways, it was like being brain-washed.

In reality, I already considered most people in league with the Evil Dictator as I thought of him. Therefore, I avoided people as if they were indeed devils and only interacted with them when absolutely necessary. I lived in a world accentuated with horror as if some SS Storm Troopers followed close behind me threatening torture and medical experiments if I were caught. Because that is how I interpreted the new data of the world, represented to me in terms of code placed in newspapers and the radio that spoke to me alone of all the millions of people in the world. It never occurred to me to question this data that suddenly presented itself to me. It seemed only reasonable that truth should be given to me alone. It seemed as clear to me that the world might be flat when all along I had information that it is round. I was as certain of this new information as if I were Ptolemy mistakenly describing the circuits of the planets and stars.

In my opinion, madness came on me suddenly. Although I had early symptoms that friends began to observe, to me the break between sanity and insanity came as a matter of a moment. I can pinpoint that minute to the very instant. I was crying. Something had upset me. Something I would have coped with in my right mind. But now my emotions had become so labile. I cried and cried and cried some more. Even I wondered why I was crying so hard. It was as

though I was engaged in an inebriated crying binge. And then I had a thought, a brief weird and poignant thought "This person has hurt me so much that I will go insane over it." I would strike at this individual for upsetting me, though in reality, it was at myself I unknowingly struck. And so it began: in that moment of unwarranted grief, I went completely and clinically insane. In effect, I announced the beginning of a psychotic episode to myself.

Without warning I began to believe the disc jockey on the radio was speaking to me. It shocked me. Could this be true? Something like this had never happened before. But now it seemed quite reasonable that it might. I never thought to question how in the world it was happening or even that it occurred. It never struck me that anything was wrong with my perspective beyond the fact that I had been wronged and now here was information confirming it.

The disc jockey seemed to relate my opinion right back at me. He played a song, "Breaking the Girl," from the rock group the Red Hot Chili Peppers. I felt vindicated. Someone else agreed that I was wronged and showed it by playing a song that spoke to that effect. So it was that the radio corroborated my feelings. A sort of coincidence became substantiated fact in the whirling insanity in my head. Of course representatives spoke to you from the radio. Can you see how tentative this relation was? But this supposed point held for me the very height of plausibility. I wondered to myself why had I never listened carefully to the radio before. In that moment of consideration, I was lost. I, as I knew myself, was gone. Long gone.

And yet many of my memories of this time remain vivid. I try to forget them as they are embarrassing and the terror of insanity is as frightening now as when it began. The memories worry me. Like epileptic fits, I worry the insanity will reoccur as if no time had passed, as if 20 years had not intervened to distance me from the consequences of irrationality. I know some people romanticize mental illness [7]. A removal of the veil of rational thought they think imprisons us in the world. This is frankly absurd. Only someone who is not a responsible psychiatrist could make such a damaging assessment.

In reality, irrationality is an invitation to hell where nothing is as it seems. There is no freedom in irrational thinking. When you cannot care for yourself or even brush your teeth regularly, when you are incredibly vulnerable to all sorts of real evil such as theft, rape or murder, the free workings of the imagination unencumbered by rational structures threaten your daily existence. Without rationality, we are unable to examine and make sense of world, of the myriad bits of data that we experience and act upon without conscious thought. Irrationality alone is as dangerous and destructive to the mind as a tornado that tears across an urban landscape. You are forced to ask, like the poet, Sylvia Plath in *Poppies in October*, "Oh my God, what am I/That these late mouths should cry open/In a forest of frosts, in a dawn of cornflowers"? [8].

Once ruptured by such an earthquake in your mind, you are forever imprisoned by the knowledge that it continues to exist underground ready to tear open a gaping hole in your existence again. I am unable to forget the cracked hermeneutical system that governed my days. Secret codes became my life. Found in all kinds of media from television, radio, to newspapers, I felt that only I (and a special Illuminati-like few) could decode their meaning. I lived for seven long months alone with only my delusions to guide me. How I paid rent on a small, dingy room and managed to appear at least semi-normal amazes me to this day. I

spent my time engaged in what I thought was deep cover as a master spy decoding messages from the shadowy organization that would alert me to secret operations and strategy against the Evil Dictator. Naturally I was a highly valued employee and most in demand. Insanity is nothing if not grandiose and vainglorious. I even went on a countrywide road trip to break down defenses that the Evil Dictator and his minions had placed in otherwise unsuspecting communities. In some respects, I felt I was successful.

See how I slip into first-person narration of the events as if they really happened? It was all so real to me that in my memory, it is not what supposedly happened but what really did. The psychotic episode lasted so long (and in a later episode continued unabated for almost a year) and was of such heightened experience, like a visit to a circus, that it feels as real to me as if it was true. I did fight against an unimaginable horror and evil that threatened my country. I was engaged in clandestine activities that led me to withdraw from my PhD program and break from all my family and friends. I feel as if the line between reality and insanity is blurred in my head. It felt so true. And that feeling remains if not the thoughts that promoted it.

For that reason, I am leery of these memories. When I approach them in depth again, the delusions make an entrance. They wander into my mind as if they had been gone only a little while and not for whole decades. Perhaps as I watch the evening news tonight, it will come to me that there is a hidden message within the supposedly objective presentation of the day's events? Perhaps I will wonder if there is a code written as if in invisible ink that I need to decipher and respond to? Maybe I will take notes again on words that strike me as important in the anchor's speech? Maybe I will search out the hidden meaning in the segments they choose to present on the news? Because I became so habituated and accustomed to this line of thought it comes back as naturally as riding a bike. What took 7 months to develop into a full-fledged world view seems to threaten me again like a destabilizing virus.

Thoughts like these remain under the surface of my conscious life like tiny ants nesting in the timber of a house. It is incumbent on me now to live with this now as there is no amount of talk or medicine that will rid me of a decay that threatens the very pillars of my mind. Yet, despite the remaining embers of irrationality, I have made so much progress. For this reason, I worry insanity will return and devastate the otherwise full plains of my mind. Memories will start the tapes running all over again. I live with this uneasiness, with the apprehension that I will lose years of back-breaking work to regain my life. I worry I will begin to attend to conversations again looking to find that nugget of information to organize my thoughts and actions on any given day. In my mind, I cringe from the idea that there is a full world of meaning hidden beneath the daily patterns of our everyday speech and concerns that occupy so much of our time. I remember too well where that deceptively interesting consideration leads.

That is why I am fully compliant with medication. Though my antipsychotic makes me feel as if my head has a bucket of concrete in its cavity rather than a brain, I endure it. Though I am cognitively impaired by more medication than a cancer patient takes, I put up with it being almost impossible to read nonfiction and with it being difficult to engage in social activities. Because in my first years of illness I often refused to take enough medication to mediate the insanity, I had to learn through bitter experience that the crippling sedation of antipsychotics is the most logical choice to be made in this predicament. Agonizing boredom is preferred

http://dx.doi.org/10.5772/intechopen.72602

over insanity. Loneliness is better than a whole host of delusions. I would rather be severely disabled than to be insane where the truth is never to be found and peace is not offered for any price. In fact, in my experience, the difficulties of psychotropic medications are well worth the trade-off in sanity. If you can accept the diminishment in your life of all you once held dear you can begin to build another world that may present its own joys, its own wonder in the end. It took me a while to learn this. But, fortunately, in time I learned it well.

It seems to me that one of the most difficult aspects of insanity was how upside down my world appeared to me at first. It was like being thrown into a lake and learning to swim or sink beneath fiery waters. I had never heard of nor had any experience with the symptoms of psychosis so when they presented I was unable to recognize them. Out of nowhere, I began to believe my phone was tapped. Soon, I thought someone or some persons were watching me. Can you imagine how disconcerting and alarming such concerns might be? These ideas seemed as legitimate to me as knowing who the president of my United States was, facts that sustained the essential background of my reality.

I even believed I fact checked them to determine their legitimacy. Did graffiti on a wall seem to have a message that spoke directly to me? Did flyers on a bulletin board acknowledge some truth about my reality? I related all this to my burgeoning belief system, and it seemed to synchronize with my concern that unknown persons were trying to communicate with me. Despite the obviously loose correlation of reference, why these people never spoke to me outright was a question I never thought to pursue. It was just a given of the situation, like rain comes from clouds—a fact you learn and expect to occur with some regularity.

Although flyers and graffiti might be twisted into any kind of significance, it seemed obvious to me that the meaning related directly to myself alone. The abbreviation for the World Wide Web (the "www" introducing any email address on a flyer) held a special significance for me. It seemed to have a connotation that lay in what seemed to be a simple play on letters and words: "www" spoke to me obscurely of World War III. I thought it contained a reference to the oncoming of a new and terrible worldwide war. To say that I was stunned and horrified, is to understate the obvious. I was in a panic. It began to dawn on me that war was on the brink of happening in what I had otherwise believed was a promising horizon and future as a history professor. All I knew about the world was wrong, and I thought if I only looked carefully enough, there was proof of what was true right beneath my nose.

The repetition of email addresses that appeared with the public unveiling of the Internet in the early 1990s alarmed me and caused me to rethink my position on what was really and even factually accurate. As it dawned on me that evil was about to enter my existence, and that of my fellow citizens, I was distraught. What was going on and how did it relate to my life, I thought? Although my understanding of the connotation of "www" was hardly reasonable or comprehensible, I was certain of its legitimacy. What do you do when you think world war is coming? Do you continue to pursue the studies you love or do you join in the offensive? Obviously, you do your duty by humanity like any other soldier in any other conflict. You pursue the defense of those you love and those in your country whom you value.

At first, I was furious with my friends and family who I sometimes thought understood everything that was happening long before I did. Why had no one informed me of the real state of

being in the world? Instead I had been allowed to live in ignorance of a terrifying massacre that loomed in the near future. It was like some dystopian nightmare. Because no one spoke to me in what I felt was an honest and direct way about the real truth of the world, it occurred to me I was being asked to be a special operative who could work *in cognito* to help save my country from the jaws of sheer evil. Again, paranoid delusions lead to big dreams. You are never just a cog in the wheel. You are the main spoke around which the rest of the world looms. A Hitler of a dictator pursued me of all the people in the world (who might or might not know they were threatened with imminent destruction).

My undergraduate degree was in English Literature. I think the critical analysis of works you learn most was my undoing in psychosis. I began to believe that structures of meaning were layered into reality as they were in a book. Deep meanings took on the most important aspect of my time trying to understand the world. In this case, I had to learn to read beneath the obvious denotation of any statement or sentence. This was exhausting. Everything I heard, everything I read, everything I saw had to be decoded for its ultimate implication. What was it trying to say to me? What was the message hidden in the puzzle for me to learn and act on in my day?

I took notes. I studied advertisements, even cosmetic banners in department stores. I actually drove around and regarded numbers and letters on license plates. And even though it seems ridiculous now, everything held meaning that I had to decode. At night, I sat home and put together the layers that had been offered to me on any particular day. From this I learned (or believed I learned) about the malevolent force bent on world conquest and that I faced horrifying dangers that included the very real threat of torture and execution. I was shocked and even horror-struck. Why had I had remained innocent to the very present dangers of this world before? I came up with a complicated answer to that question, but it only frightened me more and convinced me that my series of delusions were deeply and absolutely authentic. I never shared my belief system with others though. What kind of spy would give away their intelligence I reasoned?

I even determined that my father and sister were trying to sell me to the Saudis for medical experiments. I was pretty upset with them. In general, I was pretty upset most of the time. I felt I was pursued by evil and if it won the world would come to pieces. Really, it was like one of those video games your children play. Ironically, it would have been exciting if it were not so real, I thought. None of it seemed crazy to me. It appeared all too rational and real. Despite my education, I had absolutely no insight into my disease at all.

How else did I construct these seemingly random theories about reality as I knew it? Here is an example. In 1993, a movie came out in the United States called *The Net*, starring Sandra Bullock. She and I had shared some similar traits. We both had moderately long brown hair. We both had brown eyes and were of similar height. Can you see where this is going? Based on a few corresponding features I began to identify with her. I felt she represented me in this movie. Movie advertisements on bus stop billboards called out to me and tugged at the recesses of my mind. I decided to go see the film. Perhaps I should have been working on a paper that was dwindling in importance to me? Instead, I paid my movie money, drank the poison, and fully submitted to the full force of insanity that was to follow.

http://dx.doi.org/10.5772/intechopen.72602

In *The Net*, Sandra Bullock's character was stripped of civilization and the accoutrements of middle-class life. Her identity was stolen from her as well as her career, home and friends. In this thriller movie, she was made to live and act underground to save her life and that of the freedom of her country which was threatened by an evil CEO of a large corporation. Can you see the parallels between some of my own hard-won beliefs and that of the fate of Sandra Bullock in the movie?

After sitting through the film, I realized I was being asked to give up my comfortable life to battle evil where it showed itself in my country. Because I resembled Sandra Bullock (in my mind), it was clear I was supposed to divest myself of attachments, including family, friends and even furniture and clothing. This would allow me to be mobile like the character in the film. It was necessary to conduct guerilla warfare with no goods to tie me to a place or family relations to threaten my commitment to being a spy. I resisted for a while but finally I gave in. I made a tearful break with my relations and the university where I was so happy. Then, I gave away most of my household items and jewelry to a charity organization. It was an awful time for me. I disappeared from my life as a graduate student into the big city where I lived. No one knew where I had gone or how I was. Imagine the distress my parents experienced. I was gone for 7 months. Who knew if I was ever coming back?

However, I thought a break was necessary to prosecute war against the worst viciousness America had seen since Hitler. Following my introduction to texts within texts, I went to a lot of movies and drew similar conclusions about how to fight an under-the-table war that might damage the standing of a rising dictator. Such conclusions reminded me of Elie Wiesel in Auschwitz who said, "Could this just be a nightmare? An unimaginable nightmare … We must do something. We can't let them kill us like that, like cattle in the slaughterhouse. We must revolt." [9]. Although Jews in concentration camps were unable to revolt, I felt it was incumbent on me to fight back, to fight against the madness in the deepest of nights in my head that I only assumed was real.

To be honest, I engaged in a lot of magical thinking and ritual actions. I would say I was essentially engaged in casting spells that I thought would safeguard my well-being and threaten wickedness as it loomed. If I said a ritual incantation correctly, it would bar the Evil Dictator from acting. I spent a lot of time interpreting the code I found in newspapers and daily life, such as advertisements on display cases in stores. From this code, I extracted pieces of information that told me what words and in what order to recite them to counter the evil perpetuated by those who would oppress my nation and its vulnerable and innocent civilians. As far as I knew, I was engaged in my duty to my country for those 7 months until in the real world I was finally caught and hospitalized by the police. The only threat I presented to anyone was to myself. Violence against others was against my code of conduct.

In my altered state, I believed danger threatened me from all sides. Perhaps it is easy to see how frightened and disoriented I felt and became. Sheer panic and anxiety became my closest friends. What was left of my world was shattered with the development of the disease. As time went on, madness became more of a tyrant and ruled my hours and days like an emperor controlling his court. It was not only perceived physical danger that threatened me. There was also the severe mortification of my humanity as the disease preyed upon and destroyed my mind.

At a certain point, I decided that anyone and everyone could read my mind. Though I could not see into anyone else's head, I believed my thoughts were as visible as if seen through clear glass. Truly, this belief was daunting and disturbing. Many of our thoughts are not fit for public consumption. It is the nature of consciousness. We are torn by drives, aggressions and feelings we barely understand. Should they become public knowledge we might well be considered anathema. So the disease also ripped away at my humanity. It felt as if I was beset by devils: one day, racial epithets became engaged in my brain and from that day forward they never stopped. I was appalled. I had not heard words like this unless delivered by ignorant, bellicose morons. And I believed that everyone could hear them as I passed by. It was as true for Italians or Middle Eastern peoples. No gender was safe from the viciousness I hurled at people as I passed by. On streets I called women whores and worse. I tore into Eastern Europeans as Pollacks. I was completely unable to repress these thoughts in my head. And I thought that everyone heard them. I was mortified and distraught. I used the utmost of my energy to repress these ideas and to kill them off but it was of no avail. They occurred and recurred like hiccups, rising to the surface and bubbling forth with no help for them but to apologize profusely in their wake.

One day I took a cab ride. I decided the cab driver looked like a child molester. In my head I told him so. Naturally, I believed he heard this judgment as loud and clear as if I spoke through a megaphone. Fortunately, I was unable to register how he replied in his own brain. Notwithstanding I apologized in my head. Over and over again, I begged him to forgive me for thinking such an awful thing about a stranger who had done me no harm. Once the thought had come, it repeated itself as if on a loop. I had no control over it. I believed the thought was offered as loudly as if in spoken word. In essence, I insulted this poor man repeatedly and violently. He continued to be polite despite my repeated denigration of his looks. I was not fooled. I knew he heard me and that he was as strictly offended as I was desirous of not causing offense. This happened to me every day, and it came without warning. I found it terribly hard to bear. Essentially, I believed I was hurling damaging racial vulgarities and insults to anyone at any time on the street. I have left out the worst of these experiences as they remain unprintable. This was another reason I began to avoid people like the plague.

At once I was being asked to exist on two planes. On one level I spoke out loud to people. "Will you show me that camera in the case," I might ask? And then, since the clerk could read my mind, another thought came to me which I only believed was heard out loud. "Are you being sold as a slave to an overlord," I might conclude in my head? Whatever reply the clerk gave in spoken language would be my clue as to what I was supposed to learn from the shadowy resistance organization I worked for. This kept up month after month. After some time, the dual nature of the labor left me completely exhausted and broken down. However, although I believe I asked for it, I found no recourse, no relief; I had to run to keep up and never stop running. Also, I was no longer sleeping much. I felt on the verge of a breakdown. As I recount these memories, I remember just how painful they were and yet how absurd and outlandish they may appear today. Yet, imagine this is your very reality. You sincerely believe you have just called someone an unforgivable name. Right to their face. How do you cope with that and still feel human? I sincerely believed my humanity was being undermined and deposed. I fought vainly to retain my decency in the face of the inner violence that surrounded me at all times.

I felt keenly the breakdown in my humanity that is involved in psychosis. Not only was I besieged by a fear of physical danger in my external world, but I was overwhelmed by the changes in my mind that invaded my inner world and left me no place of safety or peace. Coming near on 7 months of uninterrupted insanity, I began to understand I was being pursued by the Evil Dictator so I could be transformed into a monster-like, zombie serial killer. This sounds like an advertisement for the year's most frightening horror flick. Instead, it was a belief that terrorized me and caused me to become frantic and desperate. I was in great danger of harming myself as I tried to avoid a fate that I thought ran me down like a shadow.

After about 5 or 6 months of psychosis, I developed anhedonia. I remember when it came on quite vividly. I was engaged on my road trip to try to save the United States from booby traps set like land mines by the Evil Dictator and his ruthless, unorthodox government. I drove from state to state across the country intent on and invested in my magical thinking where I had only to speak to dismantle snares set for an innocent population. I never knew exactly what sort of traps these might be. It never occurred to me to wonder. It was only my duty to proceed according to the information I thought accrued from codes left in the media or in spoken word by various informants (from hotel clerks to cashiers in gas stations and grocery stores). The whole world was involved in my madness and that seemed quite logical to me. I can only imagine how I presented myself to various people with whom I interacted. In essence, I was on a giant treasure hunt with a return to the status quo of the country as my golden statue.

I was driving through Utah when I first noticed the anhedonia. As I wound my way through canyons, there were picturesque or scenic pullovers on the shoulder of the freeway. I drove into one and walked out onto a cliff to view the beautiful striations of color that curved their way in rippling stripes along the canyon beyond me. I had seen pictures of Utah ravines and chasms. Now, I found myself with an opportunity to really observe them in their glory. I anticipated the joy I would find in taking a moment for myself in a day I regarded as full of hard and intense work (remember, license plates absorbed my attention at all times, I took notes on them as I drove).

Only nothing happened. I could see the mineral deposits in the side of the cliff were gorgeous. I could see the various colors that stippled the rock before me. Yet I encountered no emotional reaction in response to this view. I felt no pleasure or joy in seeing the beauty I knew was there but to which I could no longer respond to or even feel. I was astonished and sick at heart. I really began to feel my humanity was being stolen from me piece by piece. As in truth it was, but by the breakdown in my own brain not through the machinations of another. I attributed the anhedonia (a condition I had never heard of before) to plans for my utter destruction. What could I do but continue the morning along with my significant work? Although I felt like others before and after who might say, "It was like I was no longer a person," [10]. I was attuned to duty and felt its claim on me.

There were other times I experienced hallucinations that terrified me. I understood they were not real but the experience was painful nonetheless. In fact, I believed I was being tortured but I did not know how to stop it. For a while when I closed my eyes, cartoon characters appeared in the black darkness before my eyes. These characters were bright as neon strobe

lights and in all colors of a crayon box. They streamed before me back and forth like ghosts on a Halloween string. They were so bright it actually hurt my eyes. The only way I could modify or impede them was by keeping my eyes wide open no matter how fatigued I felt. Of course, this made sleep particularly difficult. And I was so afraid. I was afraid I would go blind from the intensity of the figures before me. For some time at night, I kept my eyes open until I could fall asleep from sheer and utter exhaustion.

There were also periods where I experienced strange auditory hallucinations. I knew these sounds were just as unreal as the cartoon images that plagued me. And yet in their own way, they too were frightening. I heard murmurings in back rooms that sounded like low voices on the radio. Murmur, murmur, murmur they went like a broken record, like a recording or stimulus designed to drive you insane. Many rumbling voices muttering words just below my range of hearing. I also attributed this hallucination to a form of torture. I believed the Evil Dictator was threatening me with what I might encounter next if I continued to oppose his reign and to work actively to resist him. Ironically, I believed he was threatening me with insanity. At that time, though I was sure I was sane, I was concerned that evil might undermine my grasp of reality. I continued to feel that my grip on sanity was good though in reality I was disintegrating beneath the unimpeded development of madness.

It was late into the development of schizoaffective disorder that my experience of anhedonia and these series of hallucinations led me to reason that my soul, my very humanity was under attack by the evil enemy. Over time I concluded that I was being transformed into the zombie serial killer who would roam the streets and assassinate individuals according to the will of the Evil Dictator. It seems a little bit like a Star Wars plot to me. In this case, good was being ravaged by a terrible, spreading evil. Already I could not experience beauty anymore. An afternoon breeze on my cheek left me feeling nothing. I no longer took pleasure in its soft touch through my hair. I could feel the light wind, but I did not have a reaction to it in my own heart anymore.

To be transformed into a zombie serial killer is a conclusion that sounds almost laughable when put into print. Yet, I believe it shows the propensity toward magical thinking that pervades our unconscious when no one is looking. From these experiences, I drew conclusions that led me to believe the loss of humanity I experienced was due to an external force bent on my destruction. One experience led to another until I felt that I was being threatened with becoming an inhuman creature. So that one night when I looked out a window on the ground floor of a hotel and saw a ragged drug addict or alcoholic stumbling through the street I believed he was one of those killers searching for me through darkened streets. To me he was the walking dead. It seemed a horrible confirmation of accumulated fears in which I believed I was marked for death. Some zombie assassin would savagely murder me, and then, like a vampire, my transformation into one among a vast serial killer army would be complete. I would be as devoted to the Evil Dictator as any SS officer in Hitler's army. You can see the fairy tale-like thinking that pervaded my conclusions. The good versus evil duality that defined my days. And especially the externalization of cause and effect of symptoms that were really creating havoc in my own brain.

And then one day, to my great surprise, I was what you can call sane. It happened that I was finally cornered and apprehended by the police and sometime later, fell under the care of a wonderful,

http://dx.doi.org/10.5772/intechopen.72602

caring psychiatrist who attended to my diagnosis with what was the newest and most radical psychotropic medication of the time, Risperidone. Suddenly, I could understand, I felt, I could reason again. I might end my story here but it would be the wrong position from which to close my account. It took many years and several extended periods of delusions for me to recover from mental illness. As much as one might say they are able to recover. I want to point out, however, the crucial role psychiatrists play in the recovery of sanity and humanity again after long stretches of madness. I have had two devoted psychiatrists for over 20 long years now. In this, I know I am blessed. Their long experience and strength of character have been instrumental in my recovery from delusions and return to a life beyond that of solipsistic ideas dreamt up in nightmares. I believe both of them helped me to become a better person than I was going in to psychosis.

I think my psychiatrists focused their efforts on the recovery of humanity whose loss was so traumatic for me when I was ill. Both have consistently treated me with dignity, charity and compassion. They behaved toward me as if my delusions were never an irritant or imposition. They worked as the people do who love me, with a concern for my state of mind, my happiness and my overall well-being. When I could not reason, they were the voice of reality. When I considered myself an aberration and a monster on the very edge of society, they reminded me of what I had accomplished and perhaps could achieve again in small measure. They stood by me just as a parent will and supported my dreams. They never discouraged me from being able to function at any level. They saw me through every struggle, every failure, and every time I felt lost and adrift in my world. In conclusion, they behaved toward me as if I were as important to them as a loved one is to a family member. They insisted on my humanity and sought to save my soul even when I was as torn and shredded as a sick animal.

An example may suffice. Today, my current psychiatrist is sensitive to the fact that I still feel overwhelmed by irrational fears. I believe at least some of these fears are a side effect of the dose of Risperidone. They increase or decrease with the level of the antipsychotic medication. But because of these irrational fears, cold winter snow days and icy stretches of road terrify me. I am consumed with fear of some conflagration of an accident on slick, ice-covered pavement. Although such fears have little basis in reality, my psychiatrist remains flexible if I ask to change an appointment away from a date that calls for snow. She has always reacted with kindness and sympathy if I would like to change an appointment according to the images of death and violence that crowd in on my imagination. These fears are not amenable to reason and continue to haunt me year after year.

Honestly, her response has been a great relief to me and has helped me to function better than if she ignored my plea or were uncompromising in her reaction to my very pressing fears. My psychiatrist cares for me. It shows and is significant in how I approach other people as I aspire to pick up the pieces of my life. I know she does not think of me as a freak she studies or is saddled with. This has a great impact on my confidence in reaching out to other people. It is also a balm for my heart that has been ravaged by illness. I am fragile now. Both of my psychiatrists have never questioned this fact or challenged me to rise before I could stand. Instead they have held out a hand. It is the very dignity they offer that has reached into my heart and touched my soul. In conjunction with pharmaceuticals, I believe this has laid the foundation for my return to health.

In addition, I will never forget, nor cease to be grateful for, my first psychiatrist [11]. When I first met him, I believed he was a covert member of the CIA who intended to inflict painful, Dr. Mengele-like, medical experiments on me. Of course, I was alarmed, and I hated and distrusted him on the spot. I held every grudge against him that could be imposed by a paranoid mind. In the interests of self-preservation, I meant to deceive him at every turn and to mislead him both of my intentions (at that time to harm myself) and as to how I hoped to escape what I thought were his dangerous clutches. Yet, his attitude of decency and kindness seeped into my conscious mind. He treated me with patience and kindness. He asked me questions about what I believed. He spoke quietly and reassuringly about what was going to happen to me now and how he wanted to treat me for illness. Although I was sure I was sane and that my psychiatrist was a genuine, threatening representation of evil, I made note of his apparent unconditional support. Despite myself he was soothing to me, and when medical experiments did not materialize I began to trust him.

My first psychiatrist switched my antipsychotic from Haldol (prescribed for me in a hospital) to Risperidone. The only effect Haldol had on me was to make me feel sick. But use of the Risperidone immediately had an effect and right away I began to understand something was desperately wrong with my world view. You cannot imagine how grateful I was at this turn of events. At the time, I was petrified that the end of the world was at hand. The calm manner of my psychiatrist emboldened me, and I was able to take what seemed a tremendous chance to talk to him about what I really believed was happening in the world. My psychiatrist was so quiet and unassuming. He never made a fuss or tried to force me into understanding that my belief system was illegitimate. Instead, he simply told me that what I believed to be true was a fantasy. Within a week of being on this new medication, I could see what he said was true. So I began my back breaking climb away from the valley of hell.

The point I want to make is that I haven't made that climb alone. In conjunction with my parents and psychiatrists I have forced myself to take one step after another. They were the hands that steadied me. So one leaves perdition behind, on the faith of others that you can rise. With the faith that the devil's playground is not your ultimate resting place. Without them I believe I would be less myself, less the human being I was before and who I became. It is with gratitude for kindnesses and love that I have stood up once again and planned for the refoundation of a home on fertile plains.

3. Conclusion

I write this account not to gain sympathy but in solidarity with those who remain ill, with those who find themselves on the street, who do not know the helping hand of compassion. Without a cure for the delusions I too might have become homeless and in and out of penal institutions. In my case, the police rescued me. My doctors brought about salvation and protection. Medication worked effectively for me and revived me. My parents made possible this life we have constructed together in the wake of destruction. So, I am always mindful of those who refuse treatment and remain hopelessly insane. May we remember them when we vote for politicians or city councils who support mental health treatment and outreach to those who remain in their own private corner of hell.

Conflict of interest

The authors declare that there is no conflict of interest.

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Section 2

An Update on Clinical and Treatment Approaches to Psychotic Disorders

Chapter 3

Lack of Insight in Bipolar Disorder: The Impact on Treatment Adherence, Adverse Clinical Outcomes and Quality of Life

Cătălina Angela Crișan

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.76286

Abstract

Insight is a multidimensional construct, defined as the awareness of having a mental disorder, of specific symptoms and their attribution to the disorder, the awareness of social consequences, and of need for treatment. Although insight has been studied specifically in schizophrenia and its study in mood disorders has traditionally received limited attention, the evaluation of this concept in mood disorders is also very important because of the impact on treatment compliance and outcome. In bipolar disorder (BD), clinical insight varies substantially over time. Most researchers observed that insight is more impaired during an illness episode than during remission, in mixed than in pure manic episodes, in bipolar II than in bipolar I patients, and in pure mania than in bipolar or unipolar depression. Lack of insight is a consistent factor of non-adherence to medication in bipolar patients, along with severity of BD, side effects of medication, effectiveness, and patient-related factors. Also, impaired insight into treatment and a great number of previous hospitalizations are associated with poorer clinical outcomes (psychiatric hospitalization, emergency room visits, violent or suicidal behavior) among the patients with bipolar I disorder. In the management of bipolar disorder, improving quality of life (QoL) and outcome should be one the most important goals.

Keywords: insight, bipolar disorder, adherence, quality of life, outcome

1. Introduction

In medicine, the concept of insight into madness seems to have started in early part of the nineteenth century when the clinical descriptions began to include observations about patients' awareness of their pathological state. In 1882, Pick used the term "Krankheitseinsicht" [1],

and in 1893, Krafft-Ebing used the term "insightlessness" ("in the later stages of insanity, where delusions have become organized or mental disintegration has ensued, the patient is completely insightless—(einsichtloss) about his disease state") ([2], translated by [3]). In the history of this concept, there were differences in the approach of the most important French, German, and English authors. In the French view, Pinel (1801) referred to the patient's "judgment" and to his capacity to correctly assess his state ("apprécie avec justesse son état") [4]. Baillarger separated the patients into two categories (who were and who were not insane) using insight (the patients with hallucinations, who were convinced of the reality of their hallucinations, were truly mad; on the other hand, the patients with hallucinations who realized that these hallucinations were caused by some derangement in themselves, should not be considered truly mad) [5]. A major debate concerning awareness of mental illness ("la discussion sur les aliénés avec conscience de leur état") and the responsibility of patients for criminal acts was held by the Société Médico-Psychologique in 1869–1870, and then in 1875 Billod observed that the number of patients who were aware about their state of madness was lower than those without the disease awareness [6]. He divided the patients into two categories:

1. Those who were not aware of their pathological state (they were aware of hallucinations and strange experiences but attributed those wrongly).
2. Those who were aware of their pathological state.

a. Patients with incomplete awareness (they were aware of their pathological state but, nevertheless, believed in the reality of their delusions and strange experiences).
b. Patients with complete awareness (they were aware of their pathological state and recognized the falseness of their abnormal experiences).

Billod also observed that insight is a good prognostic factor of the evolution of the disease and for illness recurrence.

Parant classified mentally ill patients, during an episode of illness, into five groups [7]:

1. Those who are aware of their acts and who can discern whether they are good or bad but are not aware of their morbid condition.
2. Those who are aware that they are in an abnormal state but do not understand or admit that this condition is a mental illness.
3. Those who are aware that their mental condition, their acts, and their ideas are the result of a mental illness, but they behave as if they would not do so (patients presenting hallucinations and delusions of persecution, being convinced by the reality of their symptoms, but who also consider themselves to be healthy).
4. Those who are aware of their condition and who understand that this condition is due to a mental illness, but who are incapable of taking an attitude in this regard.
5. Those who are aware of their condition and who understand that this condition is due to a mental illness, but who have committed or been forced to commit dangerous acts.

In the British view, Maudsley believes that the healthy man was incapable of accurately judging the behavior and the experiences of the mental ill; at the same time, the psychic patient could not judge with his healthy psychic functions the phenomenon produced by his psychically impaired functions [8]. Aubrey Lewis, in 1934, distinguished between the change in awareness and the change in judgment, both being mandatory components of the insight [9]. According to his opinion, the patient should be first aware of the change and then form an opinion, a judgment about it. Aubrey Lewis conceptualized the insight as a complex group of judgment types, based on different types of information. Lewis defined the insight as "an attitude adapted to an unhealthy change in itself, and ability to decentralize, and to give a personal judgment on one's own state."

In the German view, Pick argued that for the most part of the mental illnesses (mania, melancholia, obsessive–compulsive disorder, psychosis, dementia, alcohol abuse), the patients were somewhat aware of their affection [1]. He noted that the patients with progressive onset had a better insight time wise, unlike those for whom the disease suddenly started. Pick subdivided the concept of the disease awareness ("Krankheitsbewuβtsein") into the awareness of the phenomenon of being sick ("Krankheitsgefühl") and the disease insight ("Krankheitseinsicht").

Unlike Kraepelin and Bleuler, who did not approached the concept of the insight, Jaspers was the one who studied it for a long time and the one who brought many new elements [10]. He considered that not only the patients become conscious and develop a judgment regarding the symptoms of their illness but also the expression of their illness' symptoms is affected by the patients' awareness and judgment. Jaspers noticed that in the early stages of psychosis, the patients were uncomfortable and embarrassed, having a meaningful reaction to the lived experiences. With the disease progression, the patients tried to make sense of their own experiences, and they elaborated a delusional system. When the disease produced changes in personality, the patient's attitude to the illness was less and less understood.

Even if the concept of insight is widely used, there are important differences between authors regarding his components. In 1989, Greenfeld et al. proposed a model of insight consisting of five distinct and independent dimensions [11]: (1) views about symptoms, (2) views about the existence of an illness, (3) speculations about etiologia, (4) views about the risk of recurrence, and (5) opinions about the opportunity of treatment. This approach is focused more on patients' understanding of what is happening to them and what individual sense they are making of their experiences.

David described three distinct dimensions of insight: (1) the recognition of the presence of a mental illness, (2) the compliance with treatment, and (3) the ability to relabel psychotic symptoms (delusions and hallucinations) as pathological [12].

A more complex multidimensional model of insight is proposed by Amador et al. and consists of the following elements: (1) awareness of the signs, symptoms, and consequences of illness, (2) general attribution about illness and specific attribution about symptoms and their consequences, (3) self-concept formation, and (4) psychological defensiveness [13].

Trying to give a more practical description of the concept, Amador and Strauss proposed two important components: (1) awareness of illness and (2) attribution regarding the illness [14].

Marková [3] summarized in her monography the following components of insight: (1) an attribution of the change to pathology [10, 12, 13], (2) social consequences of illness [13], (3) views concerning etiologia and likely recurrence [11], (4) perception of changes in the self and one's interaction with the world [15], (5) need for medical treatment [12, 13, 16], (6) attitudes toward experiences [17], (7) comparison with the previous function [18], (8) predictions of performance on specific tests [19, 20], and (9) resemblance of own experiences to hypothetical cases [21].

Most studies about insight were conducted with patients suffering from schizophrenia and other psychotic disorders, neglecting patients with mood disorders. However, in the last few years, there has been an increase in interest about insight in patients with bipolar disorder [22]. The awareness of illness can be quite impaired in mania, second only to schizophrenia, even in the absence of psychosis [23].

Given the importance of insight to diagnosis, treatment adherence, and psychosocial outcome, we considered that it is appropriate to pay attention to this phenomenon. This chapter presents few remarks about the history of the concept, different models of insight, the most important psychometric tools in assessing insight and clinical implications of poor insight in patients diagnosed with bipolar disorder. Taking into account that clinical insight varies substantially over time in bipolar patients, the relationship of insight to episode subtypes and symptom dimensions is analyzed in detail. Than other important themes are addressed: the impact of unawareness of illness on non-adherence to medication, on outcome, and quality of life (QoL).

2. Measurement of insight

Over the past 15 years, semi-structured interviews with systematized scoring systems and proven psychometric strengths have been devised to measure insight. The first such measure to be used widely was The Insight and Treatment Attitudes Questionnaire (ITAQ) developed by McEvoy et al. [24]. The ITAQ has been used in large samples of patients with schizophrenia and has been shown to be reliable and valid. The questionnaire comprises 11 items designed to assess patients' recognition of illness and the need for treatment. The response of the patient is scored as 2 = good insight, 1 = partial insight, and 0 = no insight. The ITAQ employs a narrow definition of insight and does not assess many of the psychological domains that are believed to comprise insight into illness more generally.

David's Schedule for the Assessment of Insight (SAI) assesses insight based on a patient's recognition of having a mental illness, compliance with treatment, and ability to label unusual events, such as delusions and hallucinations, as pathological [12]. The Schedule for the Assessment of Insight explores insight beyond the acknowledgment of illness and the need for treatment. This measure does not, however, consider how insight may vary from symptom to symptom, nor does it consider differences between current and retrospective insight into illness.

Similarly, the Insight Scale (IS) devised by Birchwood et al. is an alternative direct translation from David's three-dimensional model of **insight, but in this case,** the empirical form is presented as a self-report measure (scoring 0–4 on each dimension, maximum: 12) [25].

Kemp and David, back in 1995, developed The Schedule for Assessment of Insight—Expanded version (SAI-E) [26], a three-dimensional scale designed to measure insight into mental illness. The questionnaire contains 10 items on three apparently separated but actually overlapped extents, as follows: the first three questions evaluate the awareness of the illness, questions 4–7 measure the capacity to relabel psychotic experiences as abnormal and the awareness of symptoms, while the latter questions rank the treatment compliance of the evaluated patient. The clinician conducts the survey by asking the patient a set of questions and then calculates the result: a higher-attained score indicates an increased level of insight.

Amador and Strauss developed the Scale to assess Unawareness of Mental Disorder (SUMD) [27], which distinguishes current and retrospective awareness of (1) having a mental disorder, (2) the effects of medication, (3) the consequences of mental disorder, and (4) the specific signs and symptoms. Since its development, this scale has gained widespread acceptance as a multidimensional measure of insight and has been validated and studied on a range of clinical samples. SUMD consists of 20 items: the first three evaluate general aspects, such as awareness of the mental disorder, of the attained effects of medication, and of the social consequences of having a mental disorder, while the latter inquire more specific topics: hallucinations, delusions, thought disorder, inappropriate affect, unusual appearance and eye contact, stereotypic or ritualistic behavior, poor social judgment and relationships, poor control of aggressive and sexual impulses, poverty of speech, flat or blunt affect, avolition, apathy, presence of anhedonia, diminished attention, and confusion-disorientation. The survey is administered by the clinician or by a trained reviewer and it can take up to 40 min. Evaluation is performed through a five-level Likert scale, a value of 0 showing intact insight.

In 1992, Carsky et al. developed Patient's Experience of Hospitalization (PEH), an 18-item self-report scale, which reflects predominantly views about being in hospital [28]. The instrument is focused on a narrow definition of denial, specifically limiting this to a failure to acknowledge: (1) having an illness or that the illness has a name or a cause, (2) any need for hospitalization, and (3) that the illness has personal impact. Each item is rated on a four-point scale of severity or level of agreement with a higher total score indicating greater denial.

Using the same concept, Marks et al. developed the Self-Appraisal of Illness Questionnaire (SAIQ) based closely on the PEH but designed for use in community settings. SAIQ is a 17-item self-report scale following the format of the PEH but substituting items about hospitalization with similar items about the need for treatment [29]. Olaya et al. developed a multidimensional scale, the Insight Scale for Affective Disorders (ISAD), a hetero-evaluation instrument for patients with mood disorders [30]. The scale evaluates dimensions like insight into illness, treatment needs, and social consequences [31]. The instrument, based on the Scale to Assess Unawareness in Mental Disorders (SUMD) [27], consists of 17 items. Scores may range from 1 (absence of symptom or full insight) to 5 (no insight) for each item, meaning

that any score above 1 indicates insight alteration for that item. This scale allows for a more complex assessment of insight, addressing BD in a comprehensive manner.

3. Clinical implications of poor insight in bipolar disorder

3.1. The relationship of insight to episode subtypes and symptom dimensions

Even if the researcher's attention was focused mainly on patients diagnosed with schizophrenia, and there is far less research on insight in bipolar disorder, a number of studies have shown that individuals with bipolar disorder frequently experience impairments in insight [32–36]. While in schizophrenia insight is viewed as more of a stable trait [37], in bipolar disorder it has been conceptualized as more of a state-dependent construct, with alterations dependent on illness phases [38–40].

Results are mixed when comparing insight of patients with schizophrenia and of bipolar patients. Some studies show that schizophrenic patients have less insight than those suffering of psychotic or mixed mania [41], while other researches show that schizophrenic patients have a similar insight deficit with patients who have been diagnosed with acute-phased bipolar disorder [32, 42–44] and to bipolar disorder with psychotic features [23, 45, 46]. The reason for the mixed results is not very clear, but one of the possible explanations could be that these studies have not taken comorbid alcohol use disorder into consideration.

Peralta and Cuesta reported in their study that the presence of psychotic features did not significantly affect insight level in manic patients at discharge from the acute ward [47]. However, Yen et al., comparing insight in-patients with schizophrenia and bipolar disorder in remission, reported that bipolar patients with psychotic features had lower levels of insight than those without psychotic features [48].

In another study, Yen et al. analyzed a cohort of 65 patients with type-I bipolar disorder and observed them over a 2-year period [49]. During this period, patients received six follow-up assessments. SAI-E was used for establishing their insight levels, along with the Young Mania Rating Scale (YMRS) and the Hamilton Rating Scale for Depression (HAM-D), for determining affective tendencies. It was observed that insight was constant during the 2-years period in continuously-stable patients. A decreased insight could be associated with the presence of the manic phase, in both single manic and repeated manic episodes. The insight returned to the pre-episodic level for patients with a single manic episode, but it remained altered in most of patients with multiple manic episodes. Depressive episodes have shown no change of insight, regardless of the number of episodes.

In 2010, Cassidy examined lack of insight in 156 bipolar patients in all phases of the illness. A total of 86 patients were evaluated during pure manic episodes, 29 during mixed manic episodes, 14 during bipolar depressed episodes, and 27 in remission [38]. The purely manic group scored a mean (SD) lack of insight of 2.39 (1.62), the bipolar depressed group had a score of 0.57 (0.85) ($p < 0.001$), while the euthymic group has shown a mean of 0.444 (0.934) ($p < 0.001$).

Differences between the mixed-manic, bipolar-depressed, and euthymic groups were null. The author findings (84.9% subjects during pure mania had scores of 1 or greater) indicated at least a moderate denial of illness in manic patients. Psychomotor agitation and irritability, both core features of mania, were predictive of lack of insight during acute episodes.

De Assis da Silva et al. included in their study from 2015 95 patients with bipolar disorder and divided them into two different groups according to the mood state presented during assessment (i.e., euthymia, mania, and depression) [36]. Insight was evaluated using the hetero-evaluation questionnaire ISAD developed by Olaya et al. [30]. Patients with bipolar disorder in mania show less insight about their condition than patients in depression or euthymia, and less insight about their symptoms than patients with depression, with the exception of awareness of weight change. The advantage of this study is that the scale used to assess insight (ISAD) is a specific scale tailored to mood disorders, which allowed the authors to conduct a detailed evaluation of insight into specific symptoms of mood disorders.

There are some longitudinal studies of insight in the acute depressive episode [23, 44, 47, 50]. These studies suggest that insight is not very impaired in the acute non-psychotic depressive episode, and that insight may increase as depression worsens. However, insight is moderately impaired in psychotic depression [23]. Insight appears to improve markedly upon acute recovery from psychotic depression.

The relationship between insight and suicidality is complex. Amador et al. [51] and Schwartz and Petersen [52] found in their studies an association between intact insight and increased risk of suicide in patients diagnosed with schizophrenia. The results are not similar when analyzing patients with mood disorders.

In 2017, throughout the year, de Assiss da Silva et al. [53] followed a group of 165 bipolar patients, 53 of whom had depressive episodes according to DSM-5 criteria. Insight was evaluated through the Insight Scale for Affective Disorder (ISAD). ISAD total scores and sub-scores based on the four factors of the scale (insight into symptoms, the condition itself, self-esteem, and social relationship were generated for the analysis. Worse total insight correlated with suicide attempt/ideation. An altered self-esteem insight was associated not only with suicidal ideation or suicide attempt but also with activity reduction and psychomotor retardation. Altered symptom-related insight correlated also with psychomotor retardation. It was shown that a better insight into having an affective disorder determines more intense hypochondriac symptoms. Worse insight into having an illness was associated with psychotic episodes. The study concluded by exposing that symptoms other than psychosis, that is, suicidal ideation, psychomotor retardation, and reduction of activity, correlate with insight impairment in bipolar depression.

Focusing on the correlation between insight level and suicidal behavior/ideation in bipolar depression, de Assiss da Silva et al. [54] observed in the same group of 165 patients who were followed during one year that a history of suicidal attempts was associated with worse insight in 60 patients with one episode of bipolar depression. No correlation between current suicidal ideation and insight level was found. The results of this study suggest that a history of suicide attempts may correlate with higher impairment of insight in bipolar depression.

3.2. The impact of insight on non-adherence

One of the greatest problems clinicians face when dealing with chronic illnesses is the effectiveness of treatment. This is influenced by different factors such as patient tolerance of the drug, the appropriateness of the regimen [55], and adherence to treatment. Studies demonstrated that antipsychotic medication reduces the severity of serious mental illness and improves patient outcomes if medicines are taken as prescribed. Medication adherence previously known as compliance [56], is a process of collaboration between the physician and the patient (if during the compliance, the physician is omniscient, the patient must strictly follow the medical prescription; in case of adherence, the patient has an active role in decision-making regarding the type of agreed medication, the way of administration, and the therapy duration). In this case, the patient may refuse to check-in for appointments or may begin to discontinue his medication. Such behavior has a negative impact on the outcome and leads to higher rates of recurrence and hospitalization [57]. The non-adherence may be deliberate (the patient reduces or stops deliberately the medication, being convinced that he does not need medication for feel good and the medication is harmful for him due to possible side effects) or unintentionally (the patient skips some medication doses, either by forgetting them or because they do not check-in in time for a new recipe).

Medication adherence is a dynamic behavior, influenced by multiple factors [58]: factors related to patients (adverse effects of medication, lack of insight), their social relationships (family support and therapeutic alliance), cognitive problems (impaired memory or attention) [59], and the system for providing health services [60]. Rates of low adherence have been reported to be as high as two-thirds in patients with schizophrenia [61]. Bipolar patients have also low rates of adherence [62–64].

In their review about adherence to antipsychotic medication in two serious psychiatric disorders, bipolar disorder and schizophrenia, Garcia et al. systematized (**Table 1**) factors common for both pathologies and specific factors by diagnosis [65].

Lack of insight seems to be the most crucial factor impacting adherence [66]. Lack of awareness may fluctuate from complete denial of illness and full rejection of the diagnosis to minimization and rationalization of symptoms along with disapproval of medication's beneficial effects, such as treating specific symptoms and minimizing the relapse risk. A considerable number of patients with schizophrenia exhibit a diminished or completely absent insight into their ailment, being more likely to completely reject their need for treatment, therefore being sustainably noncompliant. Hence, it is essential to assess patients' insight on a continuum and not just to rate it as "good" or "poor." Is the patient aware of the disease, its nature, its symptoms, and the need of undergoing antipsychotic treatment for both acute and maintenance treatment? Lacks in the capability of recognizing the presence of a mental illness and the beneficial effect of antipsychotic medication would definitely increase the likelihood of altered compliance. Also, insight has a beneficial impact over the therapeutic relationship [67].

There are several studies which proved the importance of insight (as patient-related factor) on adherence in patients diagnosed with bipolar disorder. González-Pinto et al. [68], analyzing 1831 patients with bipolar disorder (in the EMBLEM Project), found that the following

SCHIZOPHRENIA	COMMON FACTORS	BIPOLAR DISORDER
• positive symptoms • highly-severe depression at baseline • early dysphoric response • brief illness duration • presence of adverse effects (extrapyramidal syndrome, neuroleptic-induced dysphoria, akathisia, sexual impairment, weight gain) • poor therapeutic response or tolerance development • early treatment cessation rate • hostility to treatment	• low levels of education • young age • cognitive impairment • high intensity of delusional symptoms and suspiciousness • substance abuse/dependence • minority ethnicity • poor insight • poor therapeutic alliance • low socioeconomic status • barriers to treatment, bad patient experience of admission	• psychotic symptoms • highly-severe depressive episodes • presence of rapid-cycling • increased affective morbidity • comorbidities (anxiety, obsessive-compulsive disorder) • adverse effects: weight gain, cognitive impairment • longer duration of suicide attempts episodes

Table 1. Factors influencing adherence to antipsychotic medication in bipolar disorder and schizophrenia [65].

factors were significantly positively associated with good adherence: good illness awareness (good adherence from the start of treatment) and a short duration of episodes. In contrast, high scores in the Clinical Global Impressions hallucinations/delusions scale at baseline and depressive symptoms during mania were related to poor adherence.

An observational study, conducted in Europe by Novick et al. [69], included 903 patients, out of which 612 were diagnosed with schizophrenia and 291 with bipolar disorder. Its design was meant to evaluate the outcome of patients treated with two oral formulations of olanzapine over a 1-year period through several evaluation tools, as follows: Clinical Global Impression (CGI), Global assessment of Functioning (GAF), Scale to Assess Unawareness of Mental Disorder (SUMD), Medication Adherence Rating Scale (MARS), and Working Alliance Inventory (WAI). The results have shown that medication adherence had higher levels in bipolar patients (mean MARS score (SD) 6.5 (2.8)) versus schizophrenic patients (mean MARS score (SD) 5.8 (2.7)) ($p < 0.0001$). An increased insight was associated with a better treatment adherence. Higher levels of insight were related to a powerful therapeutic alliance (SCC ranging from 0.38 to 0.48, $p < 0.0001$). The research has also shown that, 1 year after the follow-up, the improvement of patients' awareness of their mental disorder (gain of insight) or an improvement in the patient-physician relationship was directly associated with a better medication adherence, an improvement of the overall functioning, and a better outcome.

Copeland et al. [70] conducted a cross-sectional survey of patients recruited into the Continuous Improvement for Veterans in Care-Mood Disorders, assessing therapeutic insight and two measures of medication adherence: the Morisky scale of interpersonal barriers and missing any doses the previous four days. A total of 435 patients were included. Greater insight into medication was negatively associated with both measures of poor adherence. Poor adherence was increased for women, African Americans, mania, and hazardous drinking. Moon et al. investigated dropout patterns and their associated factors in 275 patients with bipolar disorders who were prospectively examined for 3 years [71]. The authors observed that the dropout rates increased rapidly during the first three months and slowed after 12 months. Past psychotic symptoms, longer illness duration, past psychiatric diagnoses, and a past history of dropouts significantly influenced the time to dropout in bipolar patients. The main reasons for dropout were denial of therapeutic need and lack of treatment efficacy.

A cross-sectional study, conducted by Medina et al. [72] in five Spanish mental health community centers, was aimed to establish the various attitudes toward antipsychotics at the moment of discharge in both patients with schizophrenia and bipolar disorder and, as a secondary aim, to analyze the connection between patients' attitude and sociodemographic and clinical data. A total of 86 patients (45 with a diagnosis of schizophrenia and 41 with bipolar disorder) were initially included in the study. Patients' attitude toward treatment was assessed with the 10-item Drug Attitude Inventory (DAI-10) [73], aspects of treatment adherence with Rating of Medication Influences (ROMI) scale [74], insight with SUMD scale [27]. A total of 26% of the patients presented a negative attitude toward antipsychotic treatment (mean DAI-10 score of −4.7, SD 2.7). Most of them were diagnosed with schizophrenia. Patients with a negative attitude obtained insight scores at discharge indicative of poorer disease awareness ($r = -0.31$, $P = 0.0039$) and had a greater number of previous acute episodes.

The determinant reasons of non-adherence to medication in patients with serious mental illness were evaluated by Velligan et al. through a systematic literature review [75]. Intentional and unintentional adherence was evaluated through several indicators for each category, as follows: poor insight, disavowal toward medication, distressful effects of medication, family or social support, access to mental health-care providers, poor therapeutic alliance, and stigma for the first category and substance abuse, cognitive impairment, depression, family and social support, access to mental health care, and social functioning for the second category. A total of 20 insight-related studies (11 prospective and 9 cross-sectional) analyzed the relationship between insight and adherence. Several prospective studies have shown that a better insight, evaluated through three insight scores, was associated with an improved adherence in both schizophrenic and bipolar patients [69]. Patients with bipolar disorder presented poor awareness of their disease after acute mania treatment, associating a higher probability of non-adherence during the maintenance therapy [68]. Cross-sectional studies have shown that, in patients over 50 years old diagnosed with bipolar disorder, a poor insight is associated with non-adherence [76]. Poor insight was identified as a cause for non-adherence in more than half of the studies, followed by substance abuse, a negative attitude toward medication, side effects, and cognitive impairments. Having a negative attitude toward medication is a determinant factor of intentional non-adherence, being considered to mediate effects of insight and of the therapeutic alliance.

Taking into account the major impact that adherence to medication has on the outcome of bipolar patients and the strong correlation between three factors—awareness of illness, adherence to medication and therapeutic alliance—García et al. [65] summarize in their systematic review the potential areas for intervention to improve adherence:

- *factors associated with patients*
  - early intervention programs for young patients.
  - treatment for different dependencies (on alcohol or other drugs), encouraging cessation.
  - increase awareness of the illness and of the benefits of antipsychotic treatment through psycho-education and psychotherapy interventions.
  - prevent or minimize adverse effects of antipsychotics, personalized treatment.
  - programs and/or technical devices to support treatment adherence for patients with cognitive dysfunctions.
  - assess patient education and quality of life.
  - analyze the symptoms at onset and during the course of illness.
  - consider patient ethnicity as a potential risk factor for non-adherence
- *factors associated with pharmacological treatment*
  - explanation about treatment plan.
  - simple posology
- *factors associated with social relationships*
  - improve the patient-physician relationship.
  - involve the family in the illness of the patient
- *factors associated with the service provision system*
  - avoid patients' first contact with the health system being a traumatic experience.
  - facilitate the access to treatment and health centers.

3.3. Quality of life and its association with insight in bipolar patients.

It is important to note that the impact of insight on quality of life may be subtle during remission and may be more substantially affected in full-blown manic symptoms. Impaired insight into treatment and a greater number of previous admissions significantly increased the risk of adverse clinical outcomes with bipolar disorder.

Dias et al. evaluated in their study the relationship between insight, quality of life, and cognition in bipolar disorder [77]. A neuropsychological battery assessing attention, mental control, perceptual-motor skills, executive functions, verbal fluency, abstraction and visuospatial

attention was administered to 70 remitted bipolar patients and 50 healthy controls. No differences in quality of life and cognitive performance were observed between bipolar patients with impaired and preserved insight. Insight was found to be correlated with poorer psychological and environmental quality of life.

Gazalle et al. [78] studied 120 type-I bipolar patients (40 manic, 40 depressed, 40 euthymic), and 40 matched controls. Manic patients presented the lowest GAF measures but reported same overall QoL as euthymic patients and controls, and better QoL than depressed patients. Authors suggested that this mismatch between objective and subjective measures during acute mania may be associated with a lack of insight or awareness of their own illness.

Quality-of-life levels were compared by Yen et al. among two groups: remissive schizophrenic and bipolar patients and healthy control subjects. The impact of insight, adverse effects of medication, and use of atypical antipsychotics over the quality of life was analyzed [79]. A total of 96 subjects with bipolar disorder in remission, 96 subjects with schizophrenia in remission, and 106 healthy control subjects were included in the study. The results demonstrated that the subjects with bipolar disorder in remission had similarly poor levels of quality of life in all four domains as those with schizophrenia in remission, and both groups had poorer quality of life than subjects in control group. Insight was negatively associated with quality of life on the physical domain in schizophrenia and bipolar patients in remission. The results indicate that subjects with bipolar disorder are dissatisfied with their quality of life, even when they are in remitted state.

3.4. Insight and outcome in bipolar disorder

Research has revealed that a lack of insight is associated with poorer clinical outcomes in both schizophrenia and bipolar disorder.

Ghaemi et al. performed a study to assess the relationship between impairment in insight and long-term outcomes in affective and anxiety disorders [80]. They included 101 patients and the mean follow-up period was 3.9 months. Initial impairment in insight did not correlate with poor outcome. However, improvement in insight correlated with good outcome, particularly in bipolar disorder type I ($r = 0.56–0.67$, $P = 0.0005$).

Yen et al. followed 65 remitted bipolar I disorder patients over a 2-year period. Assessments were performed at 3, 6, 9, 12, 18, and 24 months to detect the adverse clinical outcomes defined by the incidence of bipolar-related psychiatric hospitalization, emergency room visits, and violent or suicidal behavior. Impaired insight into treatment and a greater number of previous hospitalizations significantly increased the risk for adverse clinical outcomes. However, insight into recognition of the illness and relabeling of psychotic phenomena did not have any significant effect on adverse clinical outcomes. Bipolar patients' insight into treatment is an independent predictor of adverse clinical outcomes [81].

It was shown that, in order to target a better patient outcome, treatment-related insight should be improved. The Health Belief Model, a proposed psychological model, aims to explain and predict health behaviors by focusing on individuals' attitudes and beliefs that may influence

adherence [82]. The aforementioned model stipulates that two behaviors are playing an essential role in medication acceptance, that is, patients' awareness of their condition and patients' acknowledgement of the benefits provided by their treatment adherence.

Psycho-education became a common practice in mental health settings, especially for patients diagnosed with bipolar disorder. Its aim is to increase patients' ability of managing their life during a long-term illness. Specifically designed psychological interventions for relapse prevention, associated with mood stabilizers, are useful in patients with bipolar disorder.

Most recently published psychotherapy studies describe positive maintenance results as an add-on treatment, with efficiency in the treatment of depressive episodes. Interestingly, several groups from all over the world described similar results and reached similar conclusions; almost all tested interventions contain psycho-educative tools for compliance enhancement and early identification of prodromal signs, stating the importance of a regular lifestyle, and exploring patients' health beliefs and the awareness of illness [83].

4. Conclusions

In bipolar disorder, awareness of illness is not the same in manic, mixed, or depressive episodes. In acute mania, patients lack insight, while depression, viewed either syndrome wise or dimensionally, appears to preserve insight during acute episodes. Thus, insight impairment is less severe in bipolar depression than in mania. However, psychotic depression, compared to nonpsychotic depression, is associated with a worsened insight. Evidence shows that depression-related insight might be augmented by the severity of the depressive symptoms, possibly approving the depressive realism hypothesis. Insight of remissive bipolar patients seems to be recovered. Therefore, lack of insight in bipolar disorder appears to be a mood range-related phenomenon, unlike schizophrenia.

Poor insight is associated with non-adherence. Insight impacts on the therapeutic alliance with mental health professionals (this association may be bidirectional: while insight may influence therapeutic relationship, therapeutic relationship may also influence insight). Insight, therapeutic alliance with the treating psychiatrist, and medication adherence are highly correlated in bipolar patients as in patients diagnosed with schizophrenia. The three factors covary during the course of illness and an improvement in one leads to improvements in the others. Patient's insight into treatment is a significant predictor of adverse clinical outcomes. It may be essential to include that improving insight into treatment might be a promising objective for final outcome.

At present, the usefulness of psychotherapy (family-focused therapy, interpersonal and social rhythm therapy, cognitive-behavioral therapy) for improving treatment adherence and clinical outcome of bipolar patients is unquestionable, and future treatment guidelines should promote its regular use among clinicians. As clinicians, we are responsible to offer the best treatment available to our patients, and this includes both evidence-based psycho-education programs and newer pharmacological agents.

Conflict of interest

The authors declare that they have no conflict of interest.

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Chapter 4

Negative Symptoms of Schizophrenia: Constructs, Burden, and Management

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73300

Abstract

The aim of the chapter is to raise awareness about recent constructs of negative symptoms, their burden on patients, caregivers and society, and about their management. Schizophrenia consists of positive, negative, and cognitive symptoms. However, treating physicians are not necessarily aware about recent constructs of negative symptoms, their presence at prodromal stage, and the distinction among primary, secondary, persistent, prominent, or predominant negative symptoms. Negative symptoms have a substantial impact on the day-to-day functioning of patients with schizophrenia and contribute more to impaired quality of life and poor functioning than positive symptoms do. Additionally, they are associated with high costs for society and a substantial burden for caregivers. Negative symptoms are not adequately treated by available antipsychotic therapies. Publications have shown that no antipsychotic has a beneficial effect when compared to another. Cariprazine is the only antipsychotic that has proven superiority over another antipsychotic (risperidone) in one clinical study.

Keywords: primary, secondary, prominent, predominant, negative symptoms, deficit syndrome, alogia, affect blunted, avolition, anhedonia, asociality, antipsychotic treatment

1. Introduction

It is well known and established in the scientific community that schizophrenia symptoms can be categorized as positive, negative, and cognitive. While positive symptoms are easy to recognize, negative symptoms are often more difficult to distinguish, as they can be mistaken for depressive symptoms [1, 2]. For the treatment of schizophrenia symptoms, several antipsychotics were discovered, developed, and registered from the 1950s. These drugs are efficiently

improving the positive symptoms of schizophrenia but have slight or no effect on the negative and cognitive symptoms. Since no real treatment was available for negative symptoms, little focus has been laid on this particular field of the disease so far. With very recent development approaches and the new potential treatments on the horizon, discussions on how to define, distinguish, and treat negative symptoms are increasing day by day.

Negative symptoms are a key element of schizophrenia including symptoms such as blunt affect, lack of motivation, asociality, and impoverished speech. They are associated with disruptions and/or lack of normal emotions and behavior [1, 3]. These symptoms may occur with or without positive symptoms and can, at times, be difficult to recognize as part of the disorder.

Recently, a consensus has been reached on how to describe negative symptoms [4]:

Five constructs (the 5 "A") were identified as negative symptoms namely affect (blunted), alogia, anhedonia, asociality, and avolition and were clustered into two factors: one including blunted affect and alogia and the other consisting of anhedonia, avolition, and asociality (**Table 1**). For each construct, symptoms due to identifiable factors, such as medication effects,

Blunted affect and alogia cluster	
	Affect blunted/flat affect Blunted affect refers to a decrease in emotions and expressions. Patients may appear immobile, lifeless, and have a wooden expression [5]. They may make little to no eye contact and speak in a dull monotone voice [1]. Absence of emotions is called flat affect [3]
	Alogia Patients with schizophrenia often have reduced speech and may give short answers to questions. Many questions may be required in order to receive sufficiently detailed information from the patient [3, 6]
Anhedonia, avolition and asociality cluster	
	Avolition Avolition refers to lack of motivation, sense of purpose, or ability to follow through on plans. For example, the patient may have a desire or interest to grow a garden but never act on the plan [6]
	Anhedonia Anhedonia refers to lack of pleasure. Patients suffering from schizophrenia may not take interest in activities they previously enjoyed. For example, a patient who was an avid gardener before may have a complete lack of interest in gardening when suffering from schizophrenia [5]
	Asociality/Social withdrawal Patients with schizophrenia may exhibit social withdrawal, show diminished interest and pleasure in social interactions, and often neglect activities of daily living (such as personal hygiene) [1, 3]. Asociality should not be defined in purely behavioral terms (whether the subject has social interactions and close relationships), but mainly as a reduction in motivation for social contacts (whether the subject values and desires social interactions and close social bonds) [7, 8]

Table 1. Characteristics of the most important negative symptoms.

Primary	Considered a core symptom of schizophrenia which persist during clinical stability [9]
Secondary	A consequence of positive symptoms, neurological side effects, depressive symptoms, or environmental factors [10, 11]
Deficit syndrome	Presence of at least two out of the following six negative symptoms in patients meeting criteria for schizophrenia: 1. restricted affect (referring to observed behavior), 2. diminished emotional range (i.e., reduced range of the patient's subjective emotional experience), 3. poverty of speech, 4. curbing of interests, 5. diminished sense of purpose, 6. diminished social drive for at least 12 months including periods of clinical stability. The above symptoms are primary, i.e., not secondary to factors such as anxiety, drug effect, psychotic symptoms, intellectual disability or depression [12–14]
Prominent	Prominent negative symptoms were defined as: 1. Baseline score ≥4 on at least 3, or ≥5 on at least 2 negative PANSS subscale items; or 2. PANSS negative score >3 on item 1 and item 6 and at least one third item with a score >3 and a maximum of two items with a score >3 from the positive subscale [15, 16]
Predominant	Predominant negative symptoms were defined as: 1. Baseline score ≥4 on at least 3 or ≥5 on at least 2 of the 7 negative subscale items and a PANSS positive score of <19; 2. PANSS negative score ≥6 points over PANSS positive score; 3. PANSS negative score of at least 21 and at least 1 point greater than the PANSS positive score and 4. A common sense definition, negative subscale greater than positive subscale [15, 16]
Persistent	Persistent negative symptoms are defined as the presence of at least one negative symptom of moderate or higher severity, not confounded by depression or parkinsonism, at baseline and after 1 year of treatment [17]
Liemburg—core negative symptoms	Avolition, anhedonia (Intensity of expected pleasure from activities diminished, asocial behavior) [18]
Liemburg—expressive deficit	Blunted affect, alogia (Facial expression, expressive gestures, vocal expression, spontaneous elaboration, quantity of speech diminished) [18]

Table 2. List and characteristics of frequently used negative symptom definitions.

psychotic symptoms or depression, should be distinguished from those regarded as core symptoms of the disease.

Besides this new adaptation, negative symptoms can also be characterized as primary, secondary, prominent, predominant or persistent, as deficit syndrome, or clustered as Liemburg "core negative symptoms" and "expressive deficit" clusters. **Table 2** gives an overview of frequently used negative symptom definitions.

2. Differential diagnosis

Negative symptoms can be part of various conditions/diseases and must be distinguished from those related to schizophrenia. The most important differentiation for clinical practice is between primary and secondary negative symptoms. While primary negative symptoms are considered a core symptom of schizophrenia, which persist during clinical stability [9], secondary negative symptoms are believed to be a consequence of other factors such as:

- positive symptoms (for example, social withdrawal because of paranoid ideas),
- neurological side effects of antipsychotic treatment (Parkinson like symptoms),
- depressive symptoms
- or environmental factors (social under stimulation due to hospitalization) [10, 11].

The importance of distinguishing primary from secondary negative symptoms lies in its therapeutic implication; while secondary negative symptoms can be improved by removing the underlying cause, primary negative symptoms are likely to persist despite treatment [9].

Additionally, negative symptoms, especially symptoms of **anhedonia, avolition, and asociality** can also occur in a number of other psychiatric diseases including depressive episodes, substance abuse, and internal or neurological disorders [19]. Schizoaffective disorder, depressive type (ICD-10 F25.1), and severe major depressive disorder with psychotic symptoms (ICD-10 F32.3) are two diseases that are particularly difficult to distinguish from schizophrenia with negative symptoms. Schizoaffective disorder, depressive type is "a disorder in which both schizophrenic and depressive symptoms are prominent, so that the episode of illness does not justify a diagnosis of either schizophrenia or depressive episode" [20]. The patient experiences a combination of schizophrenia symptoms, such as hallucinations or delusions, and mood symptoms, such as potentially anhedonia, avolition, and asociality. Severe major depressive disorder with psychotic symptoms is a disease where "the patient suffers from lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration is reduced, and marked tiredness after even minimum effort is common. The lowered mood varies little from day to day, is unresponsive to circumstances, and may be accompanied by so-called 'somatic' symptoms, such as loss of interest and pleasurable feelings, marked psychomotor retardation, agitation, loss of appetite, weight loss, and loss of libido. Hallucinations, delusions, psychomotor retardation, or stupor so severe that ordinary social activities are impossible" might be present [20]. A correct diagnosis and distinction from schizophrenia with negative symptoms has a great impact on therapy in these diseases: while for schizoaffective disorder and major depressive disorder the therapy includes antidepressants next to antipsychotics [21], for negative symptoms of schizophrenia, this has not been shown as effective [22].

The differential diagnosis of **blunted affect** includes next to schizophrenia, post-traumatic stress disorder (PTSD). PTSD is a mental disorder that is triggered by a terrifying event (war, torture, sexual assault). Symptoms include flashbacks, nightmares, inability to feel positive emotions, dissociative symptoms, severe anxiety, and avoidance of triggers [19]. Blunted affect, anhedonia, and feelings of detachment are also core symptoms of PTSD, which cause diminished interest in activities that produce pleasure, and reduced tendency of emotional expressions [23].

Alogia is caused by a dysfunction in the fronto-striatal area of the brain and can therefore also occur in several neurological diseases (such as Huntington's and Parkinson's diseases, dementia, etc.) [24]. However, physical symptoms that accompany such diseases make the differentiation from schizophrenia not so difficult.

Overall, it can be concluded that while symptoms of anhedonia, avolition, and asociality also occur in the course of several other diseases (especially those with depressive episodes), blunted affect and alogia seem to be more inherent to schizophrenia with negative symptoms [25].

3. Course

Schizophrenia typically begins with a prodromal period, which precedes first episode psychosis and can last from a few days to around 18 months. The prodromal period and the very early phases of the disease are characterized by negative symptoms [26]. In contrast, early stages and acute exacerbations are more characterized by positive symptoms. Over time, the positive symptoms diminish due to treatment or due to the natural course of the illness and are replaced by more prominent negative symptoms. Finally, during the residual phase of the illness, negative symptoms are most prevalent [27]. **Figure 1** shows a typical course of the disease.

Although this is a common pattern for schizophrenia, the course can vary considerably. Some patients have psychotic episodes lasting weeks or months with full remission of their symptoms between each episode; others have a fluctuating course in which symptoms are continuous but rise and fall in intensity; yet others have relatively little variation in the symptoms of their illness over time.

In order to define clinically relevant course variants, a healthcare professional needs to be able to characterize both the current state as well as the longitudinal pattern of the illness in the individual patient [28]. For this, ICD-10 provides the following course specifiers [20] (**Table 3**).

At one end of the spectrum, the person has a single psychotic episode of schizophrenia followed by complete recovery; at the other end of the spectrum is a course in which the illness never abates and debilitating effects increase (**Figure 2**).

Negative symptoms are common in the prodromal phase of the disease, in between psychotic episodes and at the end of the disease in the residual phases. According to the ICD-10, which

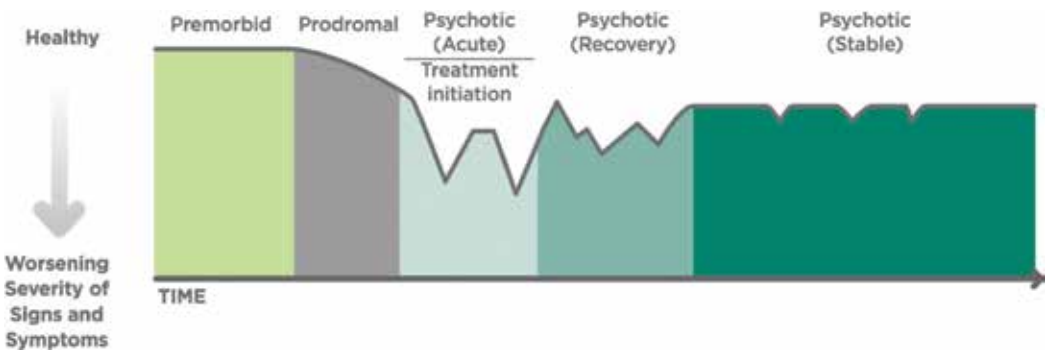

Figure 1. Individual clinical course of schizophrenia (adapted from American Psychiatric Association [32]).

Class	Course
F20.x0	Continuous; no remission of psychotic symptoms throughout the period of observation
F20.x1	Episodic; with a progressive development of "negative" symptoms in the intervals between psychotic episodes
F20.x2	Episodic; with persistent but nonprogressive "negative" symptoms in the intervals between psychotic episodes
F20.x3	Episodic (remittent); with complete or virtually complete remissions between psychotic episodes
F20.x4	Incomplete remission
F20.x5	Complete or virtually complete remission
F20.x8	Other pattern of course
F20.x9	Course uncertain, period of observation too short

Table 3. ICD-10 course specifiers.

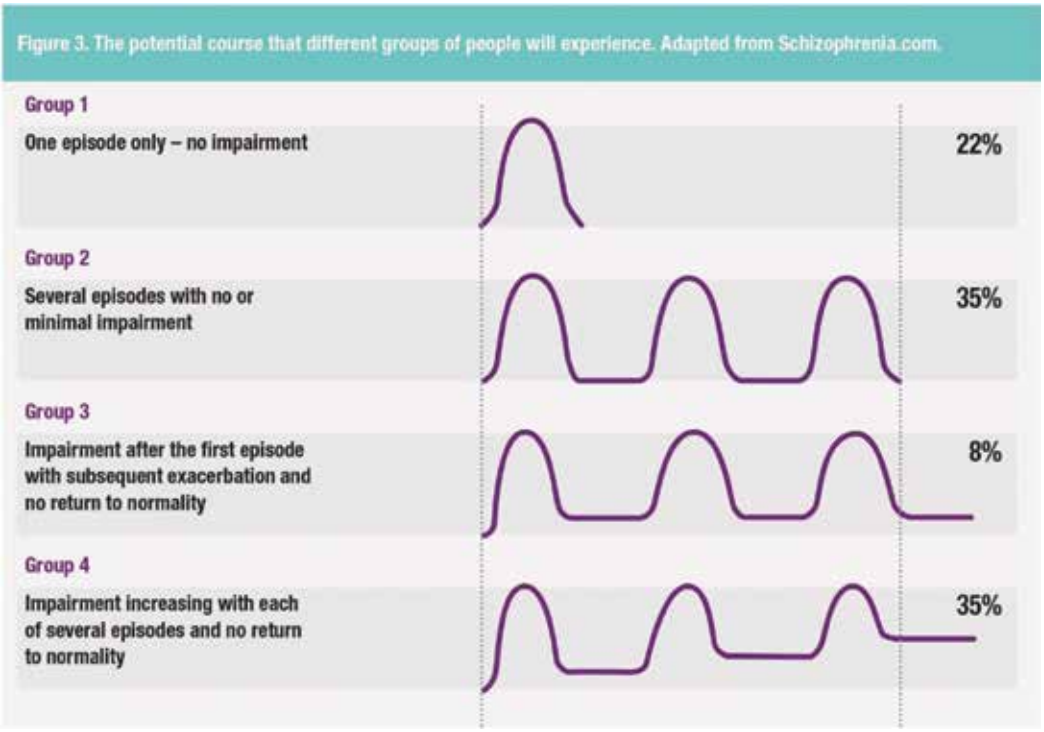

Figure 2. Overall clinical course of schizophrenia (adapted from Schizophrenia.com).

classifies schizophrenia into different subtypes (**Table 4**), negative symptoms prominently occur in hebephrenic, simple, and residual schizophrenia.

Hebephrenic schizophrenia is "a form of schizophrenia in which affective changes are prominent, delusions and hallucinations fleeting and fragmentary, behavior irresponsible and unpredictable,

F20.0	Paranoid schizophrenia
F20.1	Hebephrenic schizophrenia
F20.2	Catatonic schizophrenia
F20.3	Undifferentiated schizophrenia
F20.4	Post-schizophrenic depression
F20.5	Residual schizophrenia
F20.6	Simple schizophrenia
F20.8	Other schizophrenia
F20.9	Schizophrenia, unspecified

Table 4. Subtypes of schizophrenia according to ICD-10.

and mannerisms common. The mood is shallow and inappropriate, thought is disorganized, and speech is incoherent. There is a tendency to social isolation. Usually, the prognosis is poor because of the rapid development of 'negative' symptoms, particularly flattening of affect and loss of volition. Hebephrenia should normally be diagnosed only in adolescents or young adults" [20].

"Simple schizophrenia is a disorder in which there is an insidious but progressive development of oddities of conduct, inability to meet the demands of society, and decline in total performance. The characteristic negative features of residual schizophrenia (e.g., blunting of affect and loss of volition) develop without being preceded by any overt psychotic symptoms" [20].

"Residual schizophrenia is a chronic stage in the development of a schizophrenic illness in which there has been a clear progression from an early stage to a later stage characterized by long-term, though not necessarily irreversible, 'negative' symptoms, e.g., psychomotor slowing; underactivity; blunting of affect; passivity and lack of initiative; poverty of quantity or content of speech; poor nonverbal communication by facial expression, eye contact, voice modulation and posture; poor self-care and social performance" [20].

In summary, negative symptoms constitute a core element of the disease. They dominate the clinical picture at the beginning and at the end of the disease but are also found in between psychotic episodes.

4. Epidemiology

Historically, applying different diagnostic criteria for patients with negative symptoms has affected the incidence and prevalence numbers of such patients. Depending on the diagnostic criteria applied, negative symptoms may comprise 5–60% of patients with schizophrenia, as shown by Rabinowitz et al., who found that in a large sample of negative symptom patients, 8.1–62.3% met criteria for prominent negative symptoms and 10.2–50.2% met criteria for

predominant negative symptoms [16]. Bobes reported that approximately 60% of individuals with schizophrenia-spectrum disorders experience one or more negative symptoms [29] and about 13% of the schizophrenic patients could be described as having primary negative symptoms [29]. Buchanan claimed 15–20% experience enduring negative symptoms that are primary to the disorder [27]. In a further study by Sicras-Mainar, it was reported that 52% of the patients presented one or more negative symptoms, the most common being passive/apathetic social withdrawal and emotional withdrawal [30, 31]. Furthermore, the prevalence of negative (deficit) states has been estimated to be 15% in first episode patients, 25–30% in clinical samples and 14–17% in population studies [9].

In conclusion, it is evident that negative symptoms are highly prevalent in the schizophrenic population.

5. Risk factors

Brain imaging, electrophysiological, and oculomotor data, showing either less or different abnormalities in negative symptom patients (here defined as deficit syndrome), suggest that deficit syndrome represents a separate disease entity with respect to other forms of schizophrenia, and not just the extreme end of a severity continuum. This is further supported by evidence that deficit syndrome has different risk factors than general schizophrenia [9].

These are

- male gender—while in general schizophrenia, there is no difference in gender [9, 32]
- summer births, compared to a winter birth in general schizophrenia [9]
- serum antibodies to cytomegalovirus [9]
- low serum folate concentration [9]
- higher genetic contribution in negative symptoms than to positive symptoms [27]
- obstetric complications [33]
- structural abnormalities, such as enlarged ventricles [33]
- dysfunctional beliefs about performance (increased defeatist performance beliefs), acceptance, likelihood of success, and resources, which reduce motivation [33]

6. Burden

Negative symptoms account for much of the long-term morbidity, poor functional outcomes, and high rates of disability in patients with schizophrenia [14, 34, 35]. They have a substantial impact on the day-to-day functioning of patients affecting the ability to live independently, to perform activities of daily living, to be socially active, to maintain personal relationships, and

to work and study [16, 36–40]. Research evidence suggests that the negative symptoms of schizophrenia contribute more to impaired quality of life and poor functioning than positive symptoms do [35, 38, 41] and that their severity is associated with a lower quality of life [42].

The three major challenges of schizophrenia's negative symptoms are their modest therapeutic response, pervasiveness, and diminution of patients' quality of life and functioning [43].

Evidence suggests that even after significant improvements in psychotic symptoms, patients with schizophrenia continue to experience poor quality of life due to residual negative symptoms, depression/anxiety, or cognitive impairment [44].

Mohr et al. (using their own definition of disease states based on the PANSS, as described above) found that patients who began therapy in disease state four (high negative symptoms but low to moderate other symptoms) seemed relatively intractable to treatment, with lower odds ratios than patients starting in disease states five (cognitive impairment predominant) and seven (positive predominant) [45].

Negative symptoms are major contributors to low function levels and deterioration in most patients with schizophrenia, because poorly motivated patients cannot function at school or work, cannot maintain relationships with family and friends in the face of unresponsive affect, and do not develop personal interests when experiencing anhedonia, apathy, and inattention [43].

One longitudinal study showed that negative symptoms predicted long-term impairment in global psychosocial functioning and work performance, with negative symptom severity being a significant individual predictor of the degree of impairment in relationships [34]. Additionally, the degree of impairment in participation and enjoyment of recreational activities was significantly correlated with the severity of negative symptoms [34].

Negative symptoms affect patients' ability to cope with daily activities and have a negative impact on their quality of life. Negative symptoms are relatively common and account for much of the long-term morbidity and poor functional outcome of patients with schizophrenia.

Patients with schizophrenia have severe problems with personal and social relations, which affect their quality of life (QoL) [46]. Negative symptoms, in particular, are often enduring and lead to poor functional outcomes in individuals with schizophrenia [47]. Increased risk of suicide, an unhealthy lifestyle, poor physical health, and CV disease (which is a leading cause of death) are main reasons associated with excess early mortality in schizophrenia [31].

Negative symptoms are recognized by both the Food and Drug Administration (FDA) and European Medicines Association (EMA) as features of schizophrenia that are not adequately treated by available antipsychotic therapies and are considered a valid target for drug development [16]. Negative symptoms can often persist despite psychosocial treatments and antipsychotic medication [47, 48].

As previously discussed, increased costs are positively correlated with lower functioning and negative symptoms are the major contributor to low function levels in patients with schizophrenia. Patients with negative symptoms have been shown to use more healthcare resources (including primary care, emergency care, and specialized care visits, laboratory tests, radiology

tests, and pharmaceutical prescriptions), especially with regard to primary care visits [30]. The highest direct costs are due to a high frequency of hospital admissions in negative symptom patients [49]. In addition to this direct cost, negative symptoms represent a burden for patients, caregivers, and society and therefore constitute a relevant economic burden [30].

7. Treatment

With the development of second-generation antipsychotics, there was initially hope within the medical community of targeting the negative and cognitive symptoms, as well as the positive symptoms of schizophrenia. Indeed, various therapeutic guidelines suggest second-generation antipsychotics (SGAs) over first-generation antipsychotics (FGAs); however, this suggestion is controversial.

The second-generation antipsychotics demonstrated efficacy in treating positive symptoms with less motor side effects than first-generation antipsychotics (with accompanied improvement in secondary negative symptoms), but the treatment goal of also improving the primary, negative, and cognitive symptoms was not achieved with these medications [22].

To explore any differential efficacy against negative symptoms, Leucht et al. [50] conducted a meta-analysis of 150 RCTs that directly compared an FGA with an SGA and included data from more than 21,000 patients. They found that four SGAs (clozapine, olanzapine, amisulpride, and risperidone) were most effective overall, but also specifically with respect to negative symptoms, when compared to FGAs. The magnitude of this difference, however, was small, with the largest effect size reported being 0.32 for olanzapine. With respect to EPS side effects, these four drugs were better than high dose FGAs but not when compared to low doses. The findings of pragmatic studies comparing the clinical effectiveness of SGAs and FGAs in schizophrenia [51, 52] are consistent with the findings of Leucht et al. meta-analysis.

More recent publications have shown that no drug has a beneficial effect on negative symptoms when compared to another [53–55]. In the only meta-analysis assessing available treatments for negative symptoms versus placebo, some statistically significant differences were found for various treatments (e.g., second-generation antipsychotics, antidepressants, glutamatergic agents, psychological interventions), but no effect reached the level of clinically significant improvement [55].

The results of the Cutlass1 study showed no advantage of second-generation drugs in terms of quality of life or symptoms over 1 year in patients with schizophrenia. In fact, those participants receiving a first-generation antipsychotic did rather better. In addition, there were no significant differences in rates of objectively assessed extrapyramidal side effects [51].

Amisulpride, the most widely studied antipsychotic in patients with negative symptoms, is indicated for negative symptoms in several European countries. However, most of the evidence showing efficacy is versus placebo and was obtained from clinical trials that were conducted in the 1990s (before the introduction of the current EMA recommendations) [56–59]. When amisulpride was evaluated in two recent studies conducted in patient populations

specifically selected for predominant negative symptoms, the findings for amisulpride were equivocal [60]. A 6-month trial comparing olanzapine (5 or 20 mg/d) and amisulpride 150 mg/d with placebo only found significant improvement for low-dose olanzapine versus placebo, but not for amisulpride [61]. Additionally, in a 12-week double-blind trial comparing amisulpride and ziprasidone, equivalent improvement in negative symptoms was demonstrated for both drugs [62]. Improvement in patient functioning in conjunction with negative symptom improvement was not investigated in any of these studies [54], and pseudospecificity parameters were also not well controlled for.

Scant information is currently available to guide clinicians on the treatment of negative symptoms. This leads to

- **Treatment guidelines** rarely mentioning treatment of negative symptoms specifically, and if they do, they suggest second-generation antipsychotics. **Table 5** gives a few examples of treatment guideline suggestions. It is agreed that these antipsychotics are to be used for the treatment of negative symptoms, because so far no effective therapies were available. The scientific community agrees, however, that current antipsychotics do not adequately address negative symptoms. Therefore, it is to be shown, how therapeutic guidelines will change once an agent is available that shows better efficacy on negative symptoms than other antipsychotics.
- **Physicians prescribing** various medications including anxiolytics, antidepressants, and anticonvulsants, which sometimes add little value and create unnecessary polypharmacy [22]. Antidepressants are a common treatment choice given the overlap between predominant negative symptoms and depressive symptoms, but supporting evidence is limited [63].

In the light of these facts, it is paramount to find efficacious therapies for negative symptoms, as there is a huge unmet medical need. Extensive research is ongoing, and there are some promising agents in development that could potentially be used for negative symptom treatment later on [60, 64, 65]. However, at the moment, only one antipsychotic exists, which has shown superiority over another antipsychotic in the treatment of negative symptoms in a well-designed study examining treatment effects on primary, persistent negative symptoms and that agent is cariprazine [60].

Cariprazine is a new D3/D2 partial agonist antipsychotic with preferential binding to D3 receptors. Cariprazine differs from all available antipsychotics due to its higher affinity for D3 receptors, which is higher than that of any other antipsychotic or in fact than dopamine itself. Cariprazine can therefore affect a D3 receptor blockade [66] that no other antipsychotic can. Since the blockade of D3 receptors has been shown to be related to improvement of negative and cognitive symptoms [67], it is assumed that cariprazine's blockade of D3 receptors is responsible for its effects on negative symptoms.

This was demonstrated in a randomized, double-blind, risperidone-referenced clinical trial [60]. The study enrolled schizophrenic patients with persistent (at least 6 month), predominant (high level on negative symptoms low level of positive symptom), primary (extrapyramidal symptoms (EPS), high positive symptoms and depression were exclusionary) negative symptoms. After the 26 week treatment period, cariprazine-treated patients showed significant

Organization	Terminology	Recommendation
World Federation of Societies of Biological Psychiatry (2012)	Negative symptoms	"For primary negative symptoms, treatment with certain SGAs (amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, ziprasidone), but not with FGAs, is recommended with inconsistent evidence and with the need for more studies to prove the efficacy."
British Association for Psychopharmacology (2011)	Recommendations for the pharmacological management of negative symptoms	"Psychotic illness should be identified and treated as early as possible as this may offer some protection against the development of negative symptoms. For any given patient, the antipsychotic that gives the best balance between overall efficacy and side effects should be used."
British Association for Psychopharmacology (2011)	Where negative symptoms persist beyond an acute episode of psychosis	"To ensure EPS (specifically bradykinesia) and depression are detected and treated if present, and consider the contribution of the environment to negative symptoms (e.g., institutionalization, lack of stimulation). Consider augmentation of antipsychotic treatment with an antidepressant such as an SSRI, ensuring that choice is based on minimizing the potential for compounding side effects through pharmacokinetic or pharmacodynamic drug interactions. If clozapine is prescribed, consider augmenting with lamotrigine or a suitable second antipsychotic."
American Psychiatric Association (2010)	Negative symptoms	"Treatment of negative symptoms begins with assessing the patient for syndromes that can cause the appearance of secondary negative symptoms. The treatment of such secondary negative symptoms consists of treating their causes, e.g., antipsychotics for primary positive symptoms, antidepressants for depression, anxiolytics for anxiety disorders, or antiparkinsonian agents or antipsychotic dose reduction for extrapyramidal side effects. If negative symptoms persist, they are presumed to be primary negative symptoms of the deficit state. There are no treatments with proven efficacy for primary negative symptoms."

Table 5. Treatment guideline suggestions for negative symptoms treatment.

improvement in negative symptoms (measured by PANSS-Factor Score for Negative Symptoms /PANSS-FSNS/) and patient functionality (Personal and Social Performance /PSP/) alike compared to risperidone. Subanalyses of individual negative symptom items and PSP subdomains measuring day-to-day functioning showed that this effect was global and not only driven by selected items [60].

Responder analyses have a primary position in defining the clinical relevance of study results. In this study, these analyses with a 20 and 30% cut-off were both in favor of cariprazine over risperidone. One of the strongest methods to evaluate clinical relevance of PANSS results is the combined rate of CGI (improved/very much improved) with responder rates at 30 and 20% reduction level. Also here, cariprazine showed a clear, significant superiority of over risperidone.

The results are clinically relevant, especially bearing in mind that a significant difference over a comparator is much more difficult to achieve than over placebo, since the active comparator would be assumed to also have some activity [60].

Differences in PANSS total score, positive subscale score, general psychopathology, depression scale, or EPS scales were minimal and not statistically significant, substantiating that the change seen on negative symptoms was not due to improvement in secondary negative symptoms [60] but a true improvement on primary negative symptoms.

With no standard of care available for negative symptoms, the choice of risperidone in this study might be subject to potential criticism; however, it is the right choice considering the alternatives. Since the late 1990s, second-generation antipsychotics are the preferred treatment over first-generation antipsychotics. From the existing and available second-generation antipsychotics, only four are known to have somewhat better efficacy on negative symptoms, and these are clozapine, olanzapine, amisulpride, and risperidone [50]. Of these four:

- Clozapine is not considered a valid first-line treatment due to its severe side-effect profile. It is only a valid therapy if other antipsychotics have failed.
- Olanzapine is an effective antipsychotic medication and has, however, a completely different adverse event profile than cariprazine: its high weight gain and sedative properties would have unblinded the study. Therefore, it could not be used for this study. However, olanzapine was studied in a similarly designed negative symptom study and compared to asenapine. Olanzapine was not better in controlling negative symptoms of schizophrenia than asenapine [68], and its change from baseline to week 26 on the PANSS FSNS was lower (−7.1) than change from baseline to week 26 with cariprazine (−8.9).
- Amisulpride would have been a potential choice, since it is approved for the treatment of negative symptoms of schizophrenia in some European countries. However, which dose to choose is a challenging question: amisulpride is used in different doses for the treatment of positive symptoms (400–800 mg) and for the treatment of negative symptoms (50–300 mg) with no overlapping between the two dose ranges. Since the aim of the study was equally to improve negative symptoms and to keep positive symptoms well under control, no dose could be chosen as a well-established and empirically proven dose. Differences in equivalent doses and side-effect profiles further blurred the picture.
- Finally, risperidone was chosen, because it has a similar side-effect profile and a similar dose range to cariprazine. As no antipsychotic is considered truly better than another in the treatment of negative symptoms, risperidone is considered a valid choice and served as a representative for all antipsychotics. Risperidone kept the positive and depressive symptoms, as well as the level of EPS, well under control.

Other comparators for the study could have been placebo or aripiprazole. However,

- no empiric evidence is available for aripiprazole being an effective therapy for negative symptoms,
- and placebo would have been controversial from an ethical perspective (leaving patients untreated for 26 weeks). Moreover, such a study would have measured relapse rates instead of efficacy on negative symptoms and the results would have been difficult to interpret.

Additionally, cariprazine has demonstrated efficacy in the treatment of acute schizophrenic symptoms [44, 69, 70] as well as in relapse prevention and maintenance treatment [71]. It is generally safe and well tolerated and has a manageable safety profile. In a recent meta-analysis by Leucht et al. [72], several drugs were examined after 60 years of available antipsychotic treatment. Efficacy data on primary negative symptoms were not examined, but data on safety in the short-term acute schizophrenia trials were presented. Cariprazine showed a favorable safety profile concerning weight gain, QT prolongation, and prolactin increase [72] compared to the other antipsychotics.

8. Conclusions

Negative symptoms such as blunted affect, alogia, anhedonia, avolition, and asociality can be clustered into two main clusters: blunted affect and alogia cluster and anhedonia, avolition, and asociality cluster [4]. They can be further characterized as primary (key element of schizophrenia, and inherent to the disease) and secondary (due to external factors such as side effects, depression or positive symptoms). They affect patients' ability to cope with daily activities and have a negative impact on their quality of life.

Negative symptoms are relatively common (15–60%), and account for much of the long-term morbidity and poor functional outcome of patients with schizophrenia [16, 29–31, 68]. Despite the introduction of second-generation antipsychotics in the 1990s, the clinical management of these symptoms continued to be an unmet medical need [30]. Though these agents are very effective in managing positive symptoms of schizophrenia, they have relatively poor long-term efficacy for negative symptoms. Thus, many patients are left with negative symptoms after their positive symptoms have been partially or completely controlled [29].

Cariprazine is a new D3/D2 partial agonist antipsychotic with preferential binding, and subsequent blockade of D3 receptors [66]. Since the blockade of D3 receptors is assumed to be related to an improvement in negative and cognitive symptoms [67], cariprazine is assumed to be effective in the treatment of negative symptoms. This has been demonstrated in a well-designed clinical trial where cariprazine has shown a statistically significant improvement in negative symptoms and patient functioning compared to risperidone. Cariprazine has also shown to have an acceptable safety profile, with advantages in weight gain, QT prolongation and hyperprolactinemia compared to other antipsychotics [72].

In summary, with no antipsychotic therapies available for the treatment of primary negative symptoms, cariprazine is an exciting new potential. It could be the first-in-class compound and a game changer in the treatment of negative symptoms. With demonstrated efficacy on positive [44, 69–71] and negative symptoms [60], and a manageable safety profile, cariprazine monotherapy covers the full range of schizophrenic symptoms and could be a good long-term treatment choice for schizophrenia.

Conflict of interest

All authors are co-workers of Gedeon Richter Plc.

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Chapter 5

Interdisciplinary Rehabilitation to Facilitate Recovery of People Living with Long-Term Schizophrenia in Developing Countries

Siew Yim Loh

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75548

Abstract

Schizophrenia is characterized by irregular, alternating episodes of exacerbation and remission of psychotic symptoms. The occupational care for people living with long-term schizophrenia (PLWS) after medical treatment, for re-engagement into work, leisure, and daily-living activities, still needs attention. Personalizing follow-up care of PLWS can improve the medical-psychosocial level of patient with differing medical, physical, and psychosocial effects from their treatment exposures. This chapter highlights the call for an individual care approach that is often lacking in resource-limited countries with additional burden from entrenched stigma. Patient categorization for PLWS may be a cost-effective step forward to overcome the less effective, one-size-fits-all approach. The need to address personalized assessment of risk exposure and to remediate its consequences on function, recovery, and quality of life calls for a better interdisciplinary-care approach, and a renewed investment to ensure occupational performance after recovery. Medicine is initial, but personalized rehabilitation is warranted for much improved functioning and better quality of life. Research is also needed to evaluate and document the effectiveness of various models of interdisciplinary care for PLWS that have been developed but may not be tested/evaluated and also on models tested effective but on other long-term nonphysical conditions.

Keywords: schizophrenia, work, leisure, daily-living activities, interdisciplinary, personalized, categorizing care, occupational therapy

1. Background

Schizophrenia is recognized as a severe brain disease, with 1% of any population predicted to develop schizophrenia during their lifetime [1]. The prevalence (i.e., the number of cases in a

population at any one time point) and the incidence (i.e., the number of new cases annually) of schizophrenia is about 1% and about 1.5 per 10,000 people, with onset occurring typically during adolescence, at between 18 and 25 for men and between 25 and 35 for women [2]. The prevalence of schizophrenia in less developed countries was significantly lower than in the developed countries [3], but this difference could be due to underreporting [4]. This condition has been reported as highly unlikely to have a uniform etiology, because of the diversity of the aetiological factors involved, and the characteristically irregular and alternating episodes of exacerbation and remission of psychotic symptoms [5]. Therefore, it is considered the most disabling of all the major mental disorders and interferes with an individual's ability to think, feel and to receive, to understand sensory information, and/or how to behave appropriately.

The debilitating, public health burdens of schizophrenia also seem greater in less developed countries. About 85% of the world's population are in the 153 low- and middle-income countries [6], where 80% of people living with mental disorders reside. Mental illness accounts for 8.8% in low-income and 16.6% in lower-middle-income countries, of the total burden of disease [7, 8]. Living in a world distorted by hallucinations and delusions [9], people living with schizophrenia may feel frightened, anxious and confused, as they experience hearing voices (not heard by others), or believing that other people are reading their minds, controlling their thoughts or even trying to harm them. Their disorganized speech and behavior can be incomprehensible and may even be frightening to others. These encounters also worsen the entrenched stigma against people living with schizophrenia (PLWS), which increases the burden of care. This issue of PLWS experiencing stigma because of their illness is an ongoing battle in both developed and developing countries. They faced discrimination from many aspects of their lives including education, work, relationships and access to health-care services [10]. Studies on determinants of quality of life in schizophrenia found that gender, positive and disorganized symptoms of schizophrenia, and cognitive and physical impairments are the most important predictors of quality of life of a group of people with schizophrenia in Malaysia [11]. This issue calls for a better integrated care and a concerted public health de-stigmatization module to educate and reach more communities. It is therefore critical that medical treatment is provided with interdisciplinary rehabilitation care to address and impact these irregular, alternating episodes of exacerbation and remission and social stigma on their level of functioning in their daily living.

Occupational participation has a critical role in the recovery and functioning of people with schizophrenia. People living with schizophrenia look for treatments that relieve active symptoms and to improve their abilities to function at work, school and in their everyday lives. Research evidence suggests that occupational rehabilitative intervention can increase the likelihood of obtaining a competitive job with a positive impact on work hours, but it is often insufficient to enable optima work participation for people living with schizophrenia, and comprehensive, individualized treatments are necessary to address functional deficits which are a barrier for labor sustainability and their job performance [12]. The occupational rehabilitation for people living with long-term schizophrenia still needs attention and improvement to facilitate better social adjustment and reengagement into work, leisure and daily-living activities. However, the individual care approach is often lacking in resource-limited, developing

countries where society's entrenched stigma on mental illness aggravates and complicates the recovery of PLWS. The need to address personalized assessment of risk exposure (from long-term treatment and psychosocial exposures) and to remediate its consequences on function, recovery and quality of life warrants a renewed investment to ensure performance beyond recovery. Patient categorization for PLWS may be a step forward to overcome the less effective, one-size-fits-all approach. Therefore, this chapter highlights the call for a need to categorize care towards personalizing follow-up rehabilitation care of PLWS to improve their specific medical and psychosocial needs for each individual patient who presents with differing side effects from their long-term treatment and the long-term exposures to their environments.

Medical treatment through the use of antipsychotic medication alone in long-term schizophrenia is often not enough for the characteristically irregular and alternating episodes of exacerbation and remission of illness in schizophrenia [5]. Improving and scaling up mental health services in developing countries requires flexible policies [13], to overcome limited resources, effective inter-professional communication and evidence-based training—both in numbers and in quality university-based training for the severe shortage of health professionals like occupational therapists.

A timely initiative for developing countries with low resources is towards the development of category patient-centered, rehabilitation services—beyond the initial phase of recovery from medical treatment. Categorization of care may be a focused way to address the complex range of needs from the individual's physical health, psychosocial, financial and occupational needs in people living with schizophrenia. It is universally accepted that the standard of care for people with schizophrenia should include the combination of antipsychotic medication and psychosocial interventions [14], but in many countries, this equation is neglected due to low manpower and resources. A more concerted plan to intervene by focusing on the category of needs of people living with schizophrenia may be more cost-effective than a "one-size-fit all" approach. Categorize care for PLWS is, in simpler term, about reappraising and re-addressing, and regrouping care needs to overcome the limitations from a "one-size-fit-all" approach. The principles are based on enabling PLWS to make informed choices, received personalized care, within a philosophy of recovery and well-being [14]. Categorizing these psychosocial-care interventions can be enhanced in context-appropriate ways to offer support to PLWS such as to (1) manage with negative/positive symptom and (2) deal with negative social reactions, including from family members and occupational needs [15]. Three principles of personalized care identified—(1) categorizing care, (2) early interdisciplinary intervention and (3) comprehensiveness of care—are important concepts when the therapists attempt to rehabilitate the client (as the expert patient), in line with the patient self-management approach for chronic disease [16].

2. Categorizing care to target better functioning and quality of life

Categorizing rehabilitation care for PLWS aims to ensure sustained recovery and improve their quality of living. With a target to increase the individual's level of functioning, the rehabilitation goal is to nurture the strengths and specific life skills, and to be able to live as

independently as possible in the community [17]. The intervention targets at building up their strengths and reducing their deficits, and as such, the features of intervention program must be comprehensive, continuous, coordinated and all encompassing, to ensure better quality of living. With this, a need for more precision into the categorization of patient living with schizophrenia is warranted. This approach does require a paradigm shift in the culture of psychiatry interdisciplinary care, whereby health professionals collaborate closely towards implementing evidence-based findings (from epidemiologic knowledge and risk assessment tools) to develop a tailored, individual follow-up, and abandoning a generic approach for all people with schizophrenia. Medical and psychosocial care should eventually move into personalized precision approaches, as are recommended for all other chronic diseases too. Therefore, a care that intersect between evidence-based medicine and value-based medicine may prove to be more supportive of the patient's entitlement to autonomy, reflecting a truly commendable shift from focusing almost exclusively on a patient's clinical condition to considering him/her as a person [18]. It also sets the tone for a tailored, personalized and valued patient-centered care [19] that warrants careful identification of individual disorders, individual risk and functional needs. Studies are needed on what and how to categorize individual needs of PLWS across the spectrum of medical, psychosocial and occupational health status for a rehabilitation pathway to ensure multidimensional/comprehensive therapy where the occupational therapist can focus on value intervention to improve functional abilities and illness recovery [19]. Nevertheless, this chapter hopes to stimulate new discussions so that more studies are needed to evaluate what and how to categorize for personalized and valued care for better quality of life in people living with schizophrenia.

3. Early intervention interdisciplinary approach care

People living with schizophrenia may not present as a life-threatening condition, but early intervention should still be emphasized. Some people have only one such psychotic episode; others have many episodes during a lifetime, but even in the multi-episode group, they can lead relatively normal lives in between. Thus, any delay in medical treatment plays a significant role in the long-term outcome of these patients. The longer the duration of untreated illness, the more difficult it is to treat the patient and results in more permanent disabilities. Many have continuous or recurring pattern of illness and may not fully recover and typically requires long-term rehabilitation. Coping and self-management is needed with the symptoms of schizophrenia as they can be especially difficult for family members [16]. The numerous psychological, social and occupational dysfunctions experienced by people living with schizophrenia warrant greater comprehensive and an early therapy management, to facilitate their social functioning, and ensure a continuum of care from the hospital to their homes and community, or on the job. The occupational therapist, mental health counselors, social workers and working interdisciplinary with the psychiatrists treating these PLWS must be aware of the range of symptoms interfering with functions, so that evidence- and valued-based care can be considered for each individual.

4. Comprehensiveness of care

Comprehensiveness is defined by the institute of medicine in 1996 as "the provision of integrated, accessible health-care services by clinicians for addressing a large majority of personal health-care needs [20], but it is often refers to the bio-psychosocial or whole-person approach, that view patient as body and soul from a social context [21]". The increase in complexity of care, attending to co-morbidities and the evolution of interdisciplinary models of care calls for all health team to sustain such responsibilities and to provide better interdisciplinary care. In the comprehensive occupational therapy programs for people living with schizophrenia, the interventions planned are along the goal-directed use of time, energy and interest, with a comprehensive focus to foster adaptation, participation and performance by minimizing pathology and promoting the maintenance of health. However, in developing countries, there is a lopsided emphasis for medical personal over health-care professionals, and the low manpower of rehabilitation therapists is a significant issue for most developing countries. In Malaysia, a medical supremacy approach and an entrenched medical governance model for its health-care delivery system perpetuate the lingering issue of manpower shortages and low university-based program for training qualified occupational therapists.

5. Symptoms interfering with functions

People living with a diagnosis of schizophrenia encountered numerous dysfunctions from a serious mental illness with a very broad range of symptoms, which includes (1) "positive symptoms" (abnormal experiences), such as hallucinations (seeing, hearing, feeling something that is not actually there), delusions (false and usually strange beliefs) and paranoia (unrealistic fear); (2) "negative symptoms" (absence of normal behavior), such as emotional withdrawal and lack of motivation and enjoyment; and (3) cognitive dysfunction (problems with concentration, learning abilities and memory) [1, 2]. These symptoms also occurred with a disorganized and abnormal thinking, behavior and language. Often, they can become emotionally unresponsive or withdrawn, with the experience of progressive personality changes leading to a breakdown in their relationships with the outside world. Apart from stigma [15], the lack of insight of PLWS may be key factor contributing to the refusal of medical treatment and also medication non-adherence. At the Permai Hospital (a large mental institution in Malaysia), 54% of the patient with schizophrenia had poor insight [22], and a comparison study between patients with schizophrenia and other mood disorders psychosis found that schizophrenia patients had the worst insights—where the level of impairment of insight was associated with the functionality of patients [23]. Therefore, social isolation or withdrawal, along with the poor insights, unusual speech, thinking or behavior may precede, be seen along with or appear later on in the course of the illness. Some less obvious symptoms such as loss of interest, low energy, absence of warmth and care, and lack of humor are all dysfunctions that do not presently respond well to medications. These symptoms add to the distress for the schizophrenia sufferer and their

families. In less-developed countries, the stigmatization phenomenon (from lack of awareness) aggravates the great distress to themselves and their families. Although the outlook for people living with schizophrenia has improved over the last 25 years, this is true only in developed countries. More research is needed as the current research has gradually led to new and safer medications and unraveling the mysteries behind the causes of the disease, but the occupational rehabilitation needed to enable people to live and function with a better quality of life is still needed.

6. Physical rehabilitation

Among people living with schizophrenia, physical fitness is a fundamental rehabilitation and self-management intervention, as it preserves a sense of physical wellness and mental well-being. The sufficient amounts of moderate daily exercise also form part of a healthier daily routine and facilitate sleep pattern. Research evidence has more often than not highlighted that physical health and mental health are intertwined [24]. As schizophrenics become withdrawn and unsociable, their desire to exercises wanes. Obesity and metabolic syndrome are among the major medical co-morbidities in schizophrenia, with evidences of relationship between weight gain or metabolic syndrome and antipsychotic medications [25–27]. A study on weight changes among first-episode schizophrenia 1 year after the initiation of antipsychotic medications reported that patients treated with olanzapine had the largest mean weight gain (14+ 10 kg) with treatment [28]. Patients treated with the antipsychotics trifluoroperazine, flupenthixol decanoate and clozapine are to be associated with the highest prevalence of metabolic syndrome [29, 30]. In addition, even the normal weight people with schizophrenia have higher visceral fats compared with normal weight healthy control subjects [31], and physical activity such as simple regular walking is important and beneficial to the body composition and quality of life of PLWS [32].

7. Psychosocial rehabilitation

People with schizophrenia become ill during the critical career-forming years of life (18–35 years old), which makes them, less likely, as a group of young adults to be able to complete their certification degrees or vocational training needed for skilled work. Many have difficulty with communication, motivation, self-care and relationships with others. Together with the antipsychotic medicines to treat the symptoms of the illness, counseling and social support from family, friends and health-care services is also a vital part of therapy. Thus, many of them not only faced dysfunction from thinking and emotional difficulties but they have dysfunctions from a lack of social and work skills and experience as well. With social rehabilitation, PLWS can be very much focussed on internal processes that his/her external social world collapses [24], with a loss of self-esteem [33]. Social engagement is a longitudinal predictor of objective and subjective health [34]. In fact, evidence points to the fact that any person who is socially incompetent due to mental illness is unable to function smoothly in society because of feelings of low self-esteem, isolation and anger [35].

8. Cognitive rehabilitation

All domains of cognition are affected in schizophrenia, with verbal and visuospatial memory, attention, executive function and speed of processing most profoundly being affected [36–38]. Verbal memory represents one of the most affected cognitive domains in schizophrenia, and the impairments are the most profound [39]. Of the three symptoms domain, on positive, negative and disorganization symptom, cognition is the strongest predictor of functional outcome [40]. Cognitive deficits are closely linked to activities of daily living (ADL) and have been shown to interfere with daily functioning including activities of daily living [41], employment and quality of life [42–44]. Green et al. [45, 46] pointed out that four specific neurocognitive domains were significantly associated with functional outcomes: executive functioning, immediate verbal memory, secondary verbal memory and vigilance. Dysfunctions in activities of daily living (ADL) have been predictive of future cognitive impairment, independent of current cognitive status or depression [47, 48]. Among all ADLs, bathing impairment may have the highest risk of future institutionalization [49]. With the acknowledgement that some ADL dysfunctions are more predictive of long-term institutionalization, policymakers can plan ahead of the resources to target these declines with occupational therapy and nursing services that has implication for future program spending on long-term-care services. Functional impairment leads to an acceleration of cognitive decline [41, 48]. Therefore, any strategy to increase or maintain cognitive functioning can enable people to remain functionally independent in medical management (which is important for people living with schizophrenia) and ensure independence in their daily living [48].

9. Daily-living performance

Activities of daily living (ADL) are a part of everyday self-care activities that are important for health maintenance and independent living [41, 48, 49]. A major goal of occupational therapy rehabilitation is to enable people to develop independent living skills—for personal daily care of oneself and independent community living. ADL dependence is correlated with increased health-care costs, an increased risk of mortality, poorer quality of life and institutionalization [50–52]. Self-care including oral health has often been neglected—a cohort study on 543 people with schizophrenia found that the mean decayed-missing-filled teeth was at a high 20.5, almost double as that of the general population which was only 11.7 [53]. Wey et al. also found that higher decayed-missing-filled teeth scores were significantly associated with both older age ($p < 0.001$) and longer illness duration ($p \leq 0.048$) [53]. Leisure time is another key area of rehabilitation focus for people living with schizophrenia, who are often limited in their financial capabilities and may find it hard to know what to do with the spare time on their hands. Initial assessment must be made to determine what new skills are needed, and then from there, a program could be developed and individualized for that client [54]. Lalonde [16] reported that the leisure desires and needs of schizophrenics determine the range of activity and how they use time effectively. PLWS should be encouraged to begin/continue participating in meaningful social recreational/community activities because social engagement can help slow down the onset of ADL disability [55]. However, it is also timely for clinicians to

attend to the underlying factors that worsen ADL performance (but can be treated early such as depression, resistance to care and pain), because ADL impairment has significant ramifications for patients and leads to institutionalization and caregiver burnout.

10. Work rehabilitation

Worldwide, psychiatry disorders comprise about one-third of the burden of illness in young adulthood [56], because about 75% of adult mental health problems manifest around early adulthood [57]. Untreated mental health problems and disorders in adolescents and young adults are strong predictors of poor vocational achievements, problematic interpersonal and family functioning. Most schizophrenia rehabilitation programs need a vocational component. Financial stability is a crucial part of the rehabilitation of these young adults—and having some money in one's pocket is a potent source of self-esteem [58]. Work (paid or volunteer tasks) can become monotonous and unchallenging, but for people with schizophrenia, work can provide a social or an occupational environment/routine that is familiar and safe. A study on the quality of life of community-based chronic schizophrenia patients in Penang (Malaysia) found that people with schizophrenia experienced discrimination, social isolation and workplace exploitations [59]. A large study across 26 countries reported that 64% of PLWS (n = 469) who apply for work, training or education were discriminated [59–61]. Employment (and a task-orientated-coping style) has been found to be positively correlated with a better quality of life [62], whereby social relationship was the most impaired aspects of well-being [63] in this group where social functioning is often at risk [10]. Importantly, employment has been showed to be positively correlated with a better quality of life [64]. In short, work as a medium of rehabilitation can build up their work skills and good work habits [54], providing them with a sense of belonging, finance, meaning and purpose in life. Supported employment, a type of psychosocial therapy that offers job training, integrated together with work-related social skills training, has been used to enhance vocational and non-vocational outcomes for people with schizophrenia in mainland China [65]. Supported employment has been reported to be effective in various international settings and has a beneficial impact on competitive employment rates for about 2 years irrespective of economic conditions [66].

11. Interdisciplinary rehabilitation for schizophrenia

In the past, rehabilitation for people living with schizophrenia (PLWS) in developing countries with low resources has focus primarily on a one-size-fits-all approach, with integration of psychosocial interventions to enable these persons to engage in their highest possible level of independent functioning. Schizophrenia has been commonly associated with impairments in social and occupational functioning due to a combination of positive (hallucinations or delusions, disorganized speech) and negative symptoms (such as a flat affect or poverty of speech) and impairments in cognition (e.g., attention, memory and executive functions) [9]. In recent decades, the introduction of better, newer, more

well-tolerated antipsychotic medications has opened up possibilities for more patients to participate in psychiatric rehabilitation programs including overall patient-self-management and supported employment. The rehabilitation goals have shifted towards a better level of symptom control and management, and a greater level of subjective life satisfaction and quality of life. Therefore, an early interdisciplinary approach to plan personalized- and categorized-care intervention is based on categorizing users into smaller clusters according to their needs in line with a need-based approach to recovery [15, 18]. The therapists need to establish the level of concerns for the particular intervention—and decides with the other health-care practitioners and with clients' inter-discipline. Specific occupational therapy intervention is needed and calls for greater research as well as clinical implementation to help define the category of care packages according to the needs of occupational therapy service users and the adapted OT intervention in mental health—a preliminary framework presented in **Table 1** [63, 67]. More work and research are needed

The OT service category	Definition	Level of concerns (low, mid, high)
1. Patient self-efficacy—to engage in basic self-care, work and leisure	Adapting activities to match current abilities and thus support engagement, Focus on personal assets and resources rather than deficits only	[__] [__] [__]
2. Behavioral activation (re-motivation process)	Building enjoyment in activity engagement to make spontaneous choices to participate in self-care, leisure and work.	[__] [__] [__]
3. Self-management education to activate patients in symptom management	Increase understanding of managing the condition, and monitoring symptoms and managing changing emotions while developing coping skills	[__] [__] [__]
4. Lifestyle adjustment	An intervention that is focused on developing/establishing daily routines, roles and responsibilities in a graded pattern of intervention, leading to a structured daily routine of self-care, productivity (work) and leisure which support the delivery of life roles	[__] [__] [__]
5. Lifestyle management	Interventions focus on promoting health and prevention of ill health. Health promotion topics, that is, smoking cessation, healthier eating, mental well-being, increased physical activity addressed as part of enhancing the quality of life.	[__] [__] [__]
5. Environmental modification and assistive technology to support engagement in activity	Support with environmental modification and assistive technology and establishing a sense of purpose/direction and satisfaction in functioning in new and unfamiliar physical and social environments	[__] [__] [__]
6. Developing social relationships and networks	Building supportive social relationship at home and social engagement at the community	[__] [__] [__]
7. Enablement: back to work/meaningful occupation	Sheltered employment and into supportive employment and open employment	[__] [__] [__]

PLWS, people living with schizophrenia.

Table 1. Clustering of category of occupational therapy care progressing at a different level for PLWS.

to ensure outcome-based recovery approach. Psychosocial category of care that includes more community-based interventions must include home-based component, psychoeducation and family involvement, and some of cognitive retraining have been recommended as feasible in low-middle-income countries and self-management intervention skills training [15, 68]. In people living with schizophrenia, further category of care such as the supported employment for those who are trained with social skill has been found to be helpful in providing sustainable employment [69, 70]. The goal of interdisciplinary rehabilitation is aiming towards recovery, by facilitating and optimizing people living with long-term schizophrenia experienced by themselves as they become empowered to manage their lives. This is the rehabilitation pathway that allows them to achieve a meaningful life and one that contributes to a positive sense of belonging in the community—one that allows them to live independently, not just to exist. It calls for experts in the area of rehabilitation—in particular, the occupational therapists, psychologist and psychiatrists to collaborate directly with the "client" or the expert patient.

12. Summary

Indeed, medication is an initial must for every individual afflicted with schizophrenia, but it is by no means a cure and warrants customized rehabilitation to improve quality of life. Patient categorization for people living with long-term schizophrenia is a step forward to overcome the less-effective, one-size-fits-all approach. With more occupational therapist and psychiatrists now compared to decades ago, the rehabilitative care for PLWS needs more attention and should be improved. Occupational practice guidelines target at outcome-focused-care and interdisciplinary-care planning. It is a practice guided by the Model of Human Occupation to craft a framework that enables people to move forward—by addressing practical daily issues and gaining the needed confidence as goals are planned and achieved, and benefit from. Occupation-focused practice can transform people living with schizophrenia's daily experience of their situation, both as a patient in recovery and as a holistic human being, gradually establishing themselves as valued members of the community. Personalizing follow-up of PLWS can improve the medical and psychosocial care for each individual patient (with differing medical, physical and psychosocial exposure). In addition, personalizing care may also help reduce the entrenched stigma of psychiatry illness that still persists in many Asian cultures. There is a need to address specific (treatment, physical, psychosocial) exposures and examine combination therapies in line with developing guidelines for categories of PLWS and to evaluate the sustainability of gains beyond the rehabilitation intervention period.

In conclusion, more research work is still needed to evaluate and document the effectiveness of various models of interdisciplinary care and categorizing care for PLWS which have been developed but may not be tested/evaluated. The model tested to be effective but on other long-term non-physical conditions may also be translated and adapted for testing to ensure cost-effective deliveries. Much work is needed along a common battery of measurements (including tools for risk exposure assessments) for better comparisons across interventions and across sub-categories of PLWS. However, in resource-limited countries, strategies that

call for the social engagement of communities to support in the management of disability towards recovery and working closely with patients (and their activated families) may be ecologically more feasible. Future research should also examine the interdisciplinary partnership and communication, as well as with the community partners.

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Section 3

Neurobiology of Psychotic Disorders: Updates on Schizophrenia

Chapter 6

Genetics and Epigenetics of Schizophrenia

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75930

Abstract

Schizophrenia (SCZ) is a complex mental disorder, with a longstanding history of neurobiological investigation. It is more common in those persons who are genetically predisposed to the disorder. Since Kraepelin, psychiatrists were aware that the SCZ tended to run in families. Its heritability is up to 85%. Although the etiology of SCZ is unknown, it is now thought to be multifactorial, with multiple susceptibility genes interacting with environmental and developmental factors. There is a huge amount of genetic studies, including polymorphisms, expression, methylation, microRNAs, and epigenomics. However, identifying genes for SCZ using traditional genetic approaches has thus far proven quite difficult. Reasons for this include the complexity, heterogeneity, and comorbidity of this disorder, and also the poor definition of the clinical phenotype. Important approaches to find the relation between genotype and phenotype and may be causal genetic factors are endophenotypes and pathway analysis. However, genetic researchers need to consider carefully the models of causality they choose. There is a pathophysiological pathway that extends from genes, through proteins, neurons, neural circuits, neural regions, mental functions, external behaviors, and symptoms of SCZ. In this chapter, the genetics and epigenetics of SCZ are briefly discussed.

Keywords: schizophrenia, genetic, epigenetic, etiology, pathophysiology, endophenotype, pathway analysis

1. Introduction

Schizophrenia is a serious, disabling, and complex mental disorder, with a longstanding history of neurobiological investigation [1]. It may be one of the most disabling disorders known to human. Schizophrenia can affect anyone at any point in his or her life. It is more common in those persons who are genetically predisposed to the disorder. The first psychotic episode generally occurs in late adolescence or early adulthood and often appears earlier in

men than in women. Schizophrenia, as a common disorder, has a worldwide prevalence of around 0.3–1.0% [2]. Clinically, it is characterized by a combination of positive and negative symptoms, cognitive impairments, and disorganized behaviors.

There are 130,024 citations (110,613 papers, 17,847 reviews, and 1564 meta-analysis) related to "schizophrenia," 12,038 citations (9666 papers, 2134 reviews, and 238 meta-analysis) related to "schizophrenia gene," 1317 citations (1060 papers, 178 reviews, and 79 meta-analysis) related to "schizophrenia genome-wide association study," and 234 citations (216 papers, 11 reviews, and 7 meta-analysis) related to "schizophrenia gene enrichment" in PubMed (accessed on January 29, 2018).

Since Kraepelin delineated the disorder dementia praecox in 1899, psychiatrists were aware that the SCZ tended to run in families. Until now, there are several family studies in SCZ [3, 4]. While, the probability of developing SCZ in general population is 1%, the probability of its developing as the offspring of one parent with the disorder is approximately 17%, and the offspring of both parents with the disorder is approximately 46% [5].

A vulnerability-stress model, in which SCZ is thought to be multifactorial, with multiple susceptibility genes is interacting with environmental and developmental factors. For example, the immune response to a wide variety of bacterial or viral pathogens may be the link between prenatal infection and postnatal brain pathologies, including SCZ [6]. Additionally, intrauterine or postnatal complications with a negative impact on fetal brain development, nutritional deficiencies with effects on neurotransmitter systems, or maternal exposure to stressors are among the other important factors [7]. Identifying genes for psychiatric disorders using traditional genetic approaches has thus far proven quite difficult. Reasons for this include the complexity, heterogeneity, and comorbidity of these disorders and also the poor definition of the clinical phenotype [8]. Different studies, including MicroRNAs [9, 10], genetic polymorphisms [11, 12], gene expression [13, 14], methylation [15], and epigenomics [16, 17] are the most important genetic studies in SCZ.

2. Genetics of schizophrenia

2.1. An overview

Evidence including genetic findings shows that the early neurodevelopmental events have been implicated in the pathogenesis of disorder (**Table 1**) [1]. Traditionally, the most genetic researches on SCZ have concentrated on chromosomes and genes. These include cytogenetics, linkage, association, gene expression, and whole genome and exome scans. Although these studies have identified a number of genomic regions of interest, these have not produced any confirmed causations.

There are reasons as to why genetic approaches have met with little success in SCZ. First is that, there are no specific biological markers. Diagnostic systems, including diagnostic and statistical manuals of mental disorders (DSMs) and international classifications of diseases (ICDs), are categorical classifications and are based on interview and self-reporting of the patients. So, they are not optimal in genetic research on complex disorders. Second is the problem of

Traditional structural genetic studies	Newer structural genetic studies	Traditional functional genetic studies (gene encoding studies)	Newer functional genetic studies	Epigenetic studies
Cytogenetic studies	Genome-wide association studies (GWASs)	mRNA studies	microRNA studies	DNA modification studies
Linkage studies	Whole exome studies	Protein studies	Long noncoding RNA studies	Histone modification studies
Candidate gene association studies			Other noncoding RNA studies	
			Genome-wide expression studies	

Table 1. An overview to the genetic and epigenetic studies of schizophrenia.

genotype-phenotype relationship. After a century ago, when Wilhelm Johannsen proposed the terms "genotype" and "phenotype," our knowledge about the genetics, phenotype, and the concept of causality has evolved dramatically [18]. For example, genotype heterogeneity means that there are many genotypes that produce the same phenotype. In addition, phenotype heterogeneity means that the same genotype may produce different phenotypes. The alternate approach to find the relationship between genotype and phenotype may be endophenotypes that will be useful in detecting genes contributing to SCZ [19, 20]. However, the studies of endophenotypes (characteristics that are intermediate between the genotype and a phenotype of interest) associated with SCZ are not yet enough. Another approach may be the path analysis to identify causal variables that produce phenotypes [21, 22]. However, the chosen models of causality are very important [18]. Third is the genetic hypothesis being tested. The problems are the number of gene variants involved, the heterogeneous mechanism of the disorder, and the understanding of their interactions with the environmental and developmental factors to predisposition to SCZ. So, there is a long pathophysiological chain that extends from genes, through proteins, neurons, neural circuits, neural pools, neural regions, mental functions, external behaviors, and symptoms construct of SCZ.

By using high-throughput technologies, a huge amount of studies, including genome-wide association studies (GWASs) have reported that genetic variants, such as copy number variations (CNVs) or single nucleotide polymorphisms (SNPs) play significant roles in the pathogenesis of SCZ. In recent years, and based on the emergence of international consortia to achieve larger sample sizes, clinical, and statistically expertise and also replicable genetic findings [23], our understanding of the genetic architecture of SCZ, the number of risk variants, and their frequencies and effect sizes have been transformed. Genome-wide association studies of genetic variants have approximately tripled the number of candidate genetic loci [24]. The Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) used GWAS arrays to identify 128 independent associations spanning 108 regions. These findings demonstrate the involvement of biological processes of the brain. For example, there are associations among gene expression patterns in tissues with some roles in the immune system, providing support for the link between the immune system and SCZ [23].

2.2. Heritability

The heritability is a statistic that estimates the degree of variation in a phenotypic trait or disorder in a population that is due to genetic variation between individuals [25]. Schizophrenia is highly heritable [26] and its genetic architecture is complex and heterogeneous. Its heritability has been estimated from 81% [26] up to 85% [27], showing a non-Mendelian inheritance pattern [28]. Reported concordance rate of SCZ in monozygotic twins is about 50%; from 41–65% [27, 29], while siblings and dizygotic twins show proband concordance rates as high as 28% [27]. The risk of the general population developing the SCZ is about 0.3–1.0% worldwide [2, 30].

Evidence shows the heritability of different aspects of SCZ, such as brain region volumes [31, 32] and cognitive disabilities [33]. Thus, the combination of genetics and brain imaging (imaging-genetics approach) will be a useful strategy to assess the effects of risk genetic variants on anatomical and functional connectivities [32]. For example, the heritability in subcortical and limbic volumes ranged from 0.45 in the right hippocampus to 0.84 in the left putamen [31]. General cognitive disabilities in SCZ have also genetic contributors. By using the genome-wide complex-trait analysis (GCTA) approach, to estimate the total heritability captured by common DNA markers on genotyping arrays [34], it was shown that individuals at ultra-high risk for the disorder, relatives of the patients with SCZ spectrum disorders, and children with antecedents of SCZ may have cognitive impairments as well [33].

2.3. Candidate gene association studies

The candidate gene association study has been a major approach to discover the causative genetic factors of complex traits or disorders. Prior to the GWAS era, candidate studies were a major approach in SCZ genetics [35] and have been a pioneer in the field of genetic association studies to identify risk genetic variants associated with a particular trait or disorder [36]. These studies, including case-control and family studies, directly test the effects of genetic variants, usually CNVs or SNPs of potentially contributing genes. The candidate gene studies are relatively cheap and quick to perform, but are limited by how much is known about the biology of the disorder being investigated [37]. With the advent of rapidly changing technology, there has been an explosion of *in silico* tools available to researchers, giving them fast, efficient resources, and reliable strategies to find casual genetic variants for candidate study or GWAS [36]. Population stratification is also a major confounding factor for population-based case-control association studies and can result in false positive associations [38]. This may be solved by considering a replication study using an independent and random cohort of test and control populations or through a family study. These approaches may reduce the chance of occurrence of a similar admixture showing similar patterns of variations [39]. Prior to the advances brought about by the Human Genome Project [40], the International HapMap Project [41], and then, 1000 Genomes Project [42], it was difficult and expensive to genotype a comprehensive list of genetic variants in a genomic region. Investigators thus tended to genotype a few genetic markers in a candidate gene selected based on prevailing theories of the etiopathology of SCZ or positional candidate genes from linkage or cytogenetic studies.

The more popular hypothesis, the common disease—common variant hypothesis suggests that SCZ is associated primarily with common genetic variants [43]. Based on this hypothesis,

most of the genetic association studies have focused on these variations in SCZ. This hypothesis constitutes the rationale of GWASs, in which millions of variants, including SNPs were assessed in thousands of individuals [44, 45]. Copy number variations are sections of the genome that are repeated and the number of repeats in the genome varies between individuals [46]. Structural variations of DNA, such as CNVs, have contribution to normal genomic variability and to risk for human diseases [47]. Many studies have demonstrated that CNVs play important roles in susceptibility to SCZ [47–49].

The SZGene database (obtained 11/2017) listed 1727 candidate gene papers investigating over 1008 genes and 8788 polymorphisms. Based on published genetic association studies of SCZ, it has been reported that across 118 meta-analyses, 16 genes, including *APOE*, *COMT*, *DAO*, *DRD1*, *DRD2*, *DRD4*, *DTNBP1*, *GABRB2*, *GRIN2B*, *HP*, *IL1B*, *MTHFR*, *PLXNA2*, *SLC6A4*, *TP53,* and *TPH1* showed significant effects [50]. By using a translational convergent functional genomics approach, using candidate genetic studies, and a poly evidence scoring and pathway analyses, many genes, including *DISC1*, *TCF4*, *MBP*, *MOBP*, *NCAM1*, *NRCAM*, *NDUFV2*, *RAB18*, *ADCYAP1*, *BDNF*, *CNR1*, *COMT*, *DRD2*, *DTNBP1*, *GAD1*, *GRIA1*, *GRIN2B*, *HTR2A*, *NRG1*, *RELN*, *SNAP-25*, *TNIK,* and a few top genes, including *DISC1*, *HSPA1B*, *MBP*, and *TCF4* were identified [51]. Across meta-analyses, candidate genes, including *APOE*, *COMT*, *DAO*, *DRD1*, *DRD2*, *DRD4*, *DTNBP1*, *GABRB2*, *GRIN2B*, *HP*, *IL1B*, *MTHFR*, *PLXNA2*, *SLC6A4*, *TP53*, *TPH1*, *RELN*, *MnSOD*, *GSTM1*, *ZNF804A*, *CACNA1C*, *AN K3*, *BDNF*, *GRIN3A*, *FAAH*, *DNMT1*, *MYO18B*, *CFB*, *GRM7*, *GRM8*, *miR-137*, *MPC2,* and *CSMD1* showed nominally significant effects [11, 50, 52]. However, some of them have been questioned [35, 53–55]. A likely reason why candidate gene studies did not achieve their primary aims is inadequate statistical power. However, the considerable efforts embodied in early studies unquestionably set the stage for current successes in genomic approaches to SCZ [35].

2.4. Genome-wide association studies

A GWAS or whole genome association study (WGAS) is an approach that involves rapidly scanning genetic variants across the genomes of many people to find variations associated with a particular trait or disease. By using this approach, researchers can use the information to develop better hypotheses to detect, treat, and prevent the diseases. Such studies are particularly useful in finding genetic variations that contribute to mental disorders. Genome-wide association study searches the genome for a genome-wide set of genetic variants in different individuals to see if any variant is associated with a normal trait or a disease. This is a hypothesis-free strategy, and typically searches the genome for SNPs, or CNVs that occur more frequently in people with a particular disease than in people without the disease. Genome-wide significance is $P < 5.0 \times 10^{(-8)}$. Meta-analyses of GWAS data have begun to lead to promising new discoveries for SCZ [56]. Within the last few years, large-scale GWASs of SCZ have identified multiple risk variants with significant association with the disorder. However, these variants could explain only a small proportion of the heritability of SCZ and their effect sizes are relatively small, suggesting that more risk variants may be detected when increasing sample size in analysis [57, 58].

By the analysis of an European ancestry sample GWAS and then through a replication study, Ripke et al. [45] found significant associations for seven loci, including 1p21.3, 2q32.3, 6p21.32-p22.1, 8p23.2, 8q21.3, 10q24.32-q24.33, and 18q21.2 with SCZ. The strongest finding was with a

miRNA-137 SNP, a known regulator of neuronal development. In a meta-analysis of 18 GWASs and a replication study, Aberg et al. [3] found significant effect with SCZ for *TCF4*, *NOTCH4*, *POM121L2*, *AS3MT*, *CNNM2*, and *NT5C2* genes. By carrying out a GWAS meta-analysis, Sleiman et al. [59] found 40 SNPs in six significant loci, including *SDCCAG8*, *ITIH1*, major histocompatibility complex (*MHC*), *MAD1L1*, *CSMD1*, and *TSNARE1* genes. By analyzing two genome-wide association data sets of European-American patients with SCZ, significant associations between negative symptoms of SCZ and *BCL9*, *TMEM245*, *RNF144B*, *CTNNA3*, and *ZNF385D* genes have been detected [60]. The largest published GWAS meta-analysis of SCZ is of 34,000 patients in a meta-analysis of 52 GWASs from the Psychiatric Genomics Consortium (PGC) which identified 108 genome-wide significant loci [61]. Through large GWAS, an intronic SNP within *CSMD1* gene, rs10503253, one of the top risk SNPs for SCZ in Europeans discovered [11]. It may be concluded that the risk "A" allele is relevant to brain structure and neurocognitive functioning and these effects may be a part of the mechanism by which the *CSMD1* mediates risk for SCZ [62, 63]. By combining two SCZ cohort studies, Luo et al. [58] reported a genome-wide significant risk locus at 22q13.1. In their meta-analysis, seven SNPs on chromosome 22q13.1 reached the genome-wide significant effect, and most significant association was with SNP rs6001946 ($P = 2.04 \times 10[^{-8}]$). All seven SNPs are located in the *MKL1* gene.

It has been reported that a rare risk variation at *AKAP9* and a protective variation at *NRXN1* are in susceptibility to SCZ [64]. By doing a meta-analysis of data from the PGC and additional SCZ family sample, SNP rs4765905 in *CACNA1C* showed a strong effect [65]. Through the meta-analysis of a UK case/control study and GWAS data from the PGC, a significant effect of two *SLC30A3* gene SNPs (rs11126936 and rs11126929) was found in female subjects [66]. Chang et al. [67] in a GWAS study in Europeans (but not in Asians) found a significant effect with SCZ for *VRK2* gene SNP rs2312147. In their GWAS meta-analysis, it has been reported that rs10489202 in *MPC2* gene is significantly associated with SCZ in Han Chinese samples [68].

2.5. Gene expression studies

2.5.1. Gene encoding studies

It has been postulated that the underlying neuropathology of SCZ, at least, resides in the periodic activation of a defective genes, as a progressive process [69]. Changes in gene expression in brains of patients with SCZ have been hypothesized to reflect possible pathways related to its pathophysiology [70]. Progressive cortical reorganization and gray matter abnormalities may be pathophysiological processes in disorder [71, 72]. These changes are in parallel with changes in symptoms and cognitive impairments [73]. Epidemiological evidence suggests the widespread gene-environment interactions in the etiology of SCZ [74, 75]. So, it may be hypothesized that these interactions can alter the gene expression pattern in the brain of patients. By using the Gene Expression Omnibus Database, Karim et al. [76] showed a total of 527 differentially expressed genes of which 314 are up regulated and 213 are down regulated.

There are differences in pathophysiology of SCZ between male and female patients. It seems that the pattern of genetic architecture is different between two sexes. For example, the upregulation of 59 genes and downregulation of other 105 genes in the peripheral blood mononuclear

cells (PBMCs) from patients with SCZ have been reported [77]. By using the PBMC samples, a genome-wide expression analysis showed the alterations of gene expressions, such as *MEF2D*, *S100A12*, and *AKT1*, with immune system function [77, 78]. Additionally, in their meta-analysis, Qin et al. [13] tested for a sex by diagnosis interaction on gene expression. These authors reported that 23 genes were up regulated and 23 genes were down regulated significantly in the male group. Several of these genes, including *ATP5B*, *ATP5A1*, *MRPL23*, *AFG3L2,* and *ABCG2,* are related to energy metabolism. Four genes, including *BEX1*, *UBL4A*, *CD99*, and *MID1,* were located on sex chromosome [13]. By using a large European-wide sample in their meta-analysis, Perez-Becerril et al. [66] found the risk alleles of two *SLC30A3* variants in females, which were associated with gene expression. In a meta-analysis of 41 studies, it has been shown a significant increase in expression of pro-inflammatory genes, including *IL-1β*, *IL-6,* and *TNF-α* on transcript and protein levels in patients with SCZ [79].

2.5.2. Micro-ribonucleic acids (miRNAs) studies

These RNAs are small noncoding RNA molecules which exert their functions by pairing with messenger RNAs (mRNAs) [80] and are powerful negative regulators of gene expression [81, 82]. They function in cell proliferation and death, patterning of the nervous system, and also as modulators of target mRNA translation and stability [83], RNA silencing and post-transcriptional regulation of gene expression [84]. There are different sets of miRNAs expressed in different cell types and tissues [85] and in many other biological processes, such as insulin secretion, B-cell development [86], hematopoiesis [87], and metabolic biochemistry [81]. Aberrant miRNA expression is implicated in many disorders, such as cancers [88], ischemic heart diseases [82], and mental disorders as well. A huge amount of evidence implicates miRNAs as a class of modulator for human tumor initiation and progression [80]. However, miRNA-based therapies are under investigation. In a meta-analysis, Ma et al. [9] reported that *miR-137* genetic variant rs1625579 is significantly associated with SCZ. Additionally, in another meta-analysis of 52 GWASs completed in 2014, Hauberg et al. [10] showed that the SCZ risk genes were regulated by miRNAs ($P < 2 \times 10^{[-16]}$). The strongest miRNAs were *miR-9-5p*, *miR485-5p,* and *miR-137* [9].

2.5.3. Transcriptome and proteome studies

Transcriptome is the set of all RNA molecules (transcripts) in one cell, a population of cells or in a given organism. The study of transcriptome examines the expression level of RNAs in a given cell population, often focusing on mRNA, but sometimes including others such as transfer RNAs (tRNAs) and soluble RNAs (sRNAs).

The proteome is the entire set of proteins expressed by a genome in a cell, tissue, or organism at a certain time, under defined conditions. Proteomics is the study of the proteome. Understanding of the implication of genetic variations in mental disorders requires translation into functional effects [70]. New technologies allow the investigation of levels of mRNAs and proteins at the same time [89].

A significant increased expression of *SLC2A3*—glucose transporter, and *DAAM2*—actin assembly factor, and a significant decreased expression of *OMA1*—zinc metallopeptidase,

NLN1, and *MYBPC3*—myosin C have been reported in the first onset of SCZ [90]. The peripheral mRNA of these genes may be potential biomarkers in early stages of disorder course [89].

3. Epigenetics of schizophrenia

3.1. Epigenetics and epigenetics code

The Greek prefix *epi-* ("over") in epigenetics implies features that are "on top of" or "in addition to" the traditional genetic basis for inheritance (**Table 1**). Epigenetics is the study of changes in gene functions, including gene expression that are heritable and that does not entail a change in DNA sequence [91]. Examples of epigenetic mechanisms are DNA methylation and acetylation and also histone modifications. The epigenetic changes are potentially reversible. Epigenetic codes are heritable DNA/histone modifications that specify patterns of gene expression through differentiation and development [92].

3.2. Epigenetic study of schizophrenia

Epigenotyping might be integrated along with genotyping and phenotyping as means of implementing advanced precision medicine [93]. Epigenetic mechanisms regulate the key neurobiological and cognitive processes in the brain [94]. Epigenetic drugs, such as histone de-acetylation, and DNA methylation inhibitors have received increased attention for the management of mental disorders [95].

Neuroepigenomics represents an effort to unify the research available on the molecular pathology of mental disorders, such as single DNA methylation, to epigenome-wide association studies, post-translational modifications of histones, or nucleosomal positioning [96]. A huge amount of studies examining the role of epigenome, including epigenetic signaling, such as DNA and histone modifications in the etiology of SCZ was published [97, 98]. Large-scale consortia, such as the PGC and the Common Minds Consortium provide detailed insight into the epigenetic risk architectures of SCZ [99]. However, the absence of consistently replicated genetic effects together with changes in gene expression suggests the role of epigenetic mechanisms in SCZ [16].

Brain development is guided by interactions between the genome and environment, such as early life adversity. Epigenetic mechanisms can mediate these interactions and increase the risk of SCZ [17]. In a mixed model of SCZ risk, abnormal epigenetic states with large effects are superimposed on a polygenic liability to SCZ [100]. It has been reported that several genes related to nucleosome and histone structure are dysregulated in PBMC of patients with SCZ. It may be suggesting a potential epigenetic mechanism underlying the risk factor for the development of SCZ [101].

Genome-scale mapping of epigenetic mechanisms, including chromosomal loopings, and other epigenetic determinants of genome organization help to understand the mechanisms contributing to dysregulated expression of synaptic and metabolic genes in SCZ [102]. Some authors have found methylation differences in different genes, including *COMT*, *RELN*, and in some other genes implicated in dopaminergic, serotoninergic, γ-aminobutyric acid (GABA)ergic, and glutamatergic pathways [103]. It has been proposed that prenatal stress induces neurodevelopmental

alterations in the prefrontal cortex that are expressed as cognitive impairments observed in SCZ [104]. Reelin (*RELN*) is involved in cortical neural connectivity and synaptic plasticity. Downregulation of *RELN* expression due to its hypermethylation has been associated with epigenetic changes in this gene of the prefrontal cortex of patients with SCZ [97].

A significant portion of patients with SCZ shows deficits in glutamate decarboxylase 1 (*GAD1*). This gene encodes a 67 kDa glutamate decarboxylase (*GAD67*) protein in multiple areas of adult cerebral cortex. This event, possibly reflecting molecular defects in subtypes of GABAergic interneurons essential for network synchronization and cognition [105]. Dysfunction of prefrontal cortex in SCZ includes the changes in GABAergic mRNAs, including decreased expression of *GAD1*. It has been demonstrated that the methylation frequency at CpG dinucleotides located at the proximal *GAD1* promoter shows a significant deficit in repressive DNA methylation in patients with SCZ [106]. Adverse life events have been found to control DNA methylation in postmitotic neurons. This phenotype in SCZ was accompanied by a persistent increase in *AVP* gene expression [107].

4. Pathway analysis

4.1. An overview

The concept of pathway is more complex structure than a cluster. Pathways in biology correspond to series of interactions among different molecules in a cell that lead to a certain product. Pathway-based analysis provides a technique, which allows a comprehensive understanding of the molecular mechanisms underlying complex traits or disorders, such as mental disorders. There are a variety of pathway-based approaches, including SNP/GWAS-derived pathway analysis, which correspond to different research designs and data types [108].

In pathway analysis, data come from high throughput biology. Gene sets corresponding to biological pathways are tested for significant relationships with a phenotype. Genotyping, gene expression arrays, or any data elements that could be mapped to genes or gene products could be used. It may be concluded that the pathway analysis represents a potentially powerful and biologically-oriented bridge between genotypes and phenotypes [109]. Pathway analysis has become the first choice for gaining insight into the underlying biology of differentially expressed genes and proteins, as it reduces complexity and has increased explanatory power [110].

4.2. Pathway analysis in schizophrenia

By using the key words of "genome-wide association study" in PubMed database, over 22,000 human GWAS publications have described genetic associations to a wide range of disorders and traits. Additionally, by using the key words of "genome-wide association study and schizophrenia" in PubMed, more than 1190 human GWAS publications have described genetic associations to SCZ. Genome-wide data sets are increasingly viewed as foundations for discovering pathways and networks relevant to phenotypes [111]. However, extending GWAS findings to mechanistic hypotheses about the development of SCZ has been a major ongoing challenge.

Sundararajan et al. [22] have been used the clinically relevant and reported susceptibility genes associated with SCZ and available gene analysis program, and created a molecular profile of the updated SCZ genes. These genes were predominantly expressed in specific brain regions, including the cerebellum, cerebral cortex, medulla oblongata, thalamus, and hypothalamus. Interestingly, by the analysis of major biological pathways and mechanisms associated with SCZ genes, these authors identified glutaminergic, serotonergic, GABAergic, and dopaminergic receptors, calcium-related channels, solute transporters, and neurodevelopmental genes. Biological mechanisms, including synaptic transmission, membrane potential, and transmembrane ion transport regulation were identified as leading molecular functions associated with SCZ genes [22].

Regarding the involvement of neuroinflammation in pathogenesis of SCZ in postmortem brains of patients with SCZ, neuroinflammatory markers and an overall increase in expression of pro-inflammatory genes have been reported [79].

By using a translational convergent functional genomics approach and a poly evidence scoring and pathway analyses, Ayalew et al. [51] identified top genes (e.g., *DISC1*, *HSPA1B*, *MBP*, and *TCF4),* brain development, myelination, cell adhesion, glutamate receptor signaling, G-protein coupled receptor signaling, and cAMP-mediated signaling as key to pathophysiology and as targets for therapeutic intervention.

Karim et al. [76] carried out pathway and gene ontology analyses and observed alteration in a few signaling pathways in neurons. These pathways were GABA receptor, immune response, G beta gamma, dopamine and cyclic AMP, complement system, axonal guidance, dendritic cell maturation, *CREB*, and interleukin-1 signaling pathways and networks.

By using the network-based approach for evaluating gene co-expression, Mistry et al. [112] found separate gene co-expression networks. Functional enrichment analysis showed that altered genes expression in SCZ associate with biological processes such as oxidative phosphorylation, myelination, synaptic transmission, and immune function [112].

Differentially expressed genes in PBMC of patients with SCZ have been reported that were involved in pathways such as cell adhesion, neuronal guidance, neurotrophins, oxidative stress, glucose metabolism, apoptosis, and cell-cycle regulation [78].

It has been suggested that the genetic basis of SCZ has a complex evolutionary history. It has been hypothesized that the genetic architecture components of SCZ are attributable to human lineage-specific evolution [113]. It has been shown that the SCZ genes are located near previously identified human accelerated regions (HARs). Additionally, these genes enrich in a GABA-related co-expression module significantly. These genes are differentially regulated in patients with SCZ. It has been concluded that genes located near the HARs are associated with important functional roles in the genetic architecture of SCZ [113].

Cell death is an active process that maintains tissue homeostasis. Three types of distinct cell death are apoptosis, autophagic cell death, and necrosis [114]. The apoptotic pathway will begin with death receptor activation. This activation leads to the formation of death receptor signaling pathways, resulting in the demolition of the cell [115]. It has been hypothesized that

an increase in apoptosis may underlie neuropathology of SCZ [116]. There are significant expression changes in death genes receptor signaling pathways in the dorsolateral prefrontal cortex of patients with SCZ, including the *TNFSF13* and *TNFSF13*. It has been concluded that the increased *TNFSF13* expression may be one of the abnormalities that contribute to the brain pathology in SCZ [116].

By using the factor analysis of symptoms of narrowly defined patients with SCZ through the clinician-rated operational criteria checklist items in an Irish family sample, implemented genome-wide association, gene-based, and gene-pathway analyses of these SCZ-based symptom factors, Docherty et al. [117] could find three factors, including: a manic, a depressive, and a positive symptom factor. Gene-based analysis of these factors showed *PTPRG* and *WBP1L* genes. These genes were also implicated by the PGC study of SCZ [45]. It has been suggested that variants in these two genes might also act as modifiers of SCZ symptoms. Gene pathway analysis of the mania factor indicated over-representation of glutamatergic transmission, GABA-A receptor, and cyclic GMP pathways and these pathways may have differential influence on affective symptoms in SCZ [117].

Through the interrogating SCZ genes and their complex interactions at various levels, including transcripts and proteins and also environmental and developmental factors, our knowledge and insight into the disorder processes will increase. This may possibly open the new avenues for more effective therapeutic interventions.

5. Future perspective

Although a huge amount of studies has been performed and significant progress has been made in past decades, the high heritability, phenotype heterogeneity, and strong genetic and epigenetic heterogeneity of SCZ still post as major challenges to the genetic dissection of this complex syndrome. Therefore, more studies are needed to explain its missing heritability [118]. It is essential to shift paradigm in understanding the etiopathology of SCZ. A critical question is "What is schizophrenia?" Is it a specific disorder or a heterogeneous syndrome? Changes in brain gene expression of the patients with SCZ may reflect the possible pathways related to pathophysiology of the syndrome.

A few suggestions for the next decade are studying the multiple brain regions in normal people to better understand neural circuitry, genetics and epigenetic patterns of the brain, peripheral biomarker studies, and analyze the other omics data, such as transcriptomics across a developmental series of brains. System biology and computational approaches will be useful to advance from normal brains to a more reliable and valid definition of the SCZ interactome and connectome [70].

Through the better understanding of pathophysiology of SCZ, at the levels of genetic and epigenetic, we could identify new leads for the management of this complex syndrome. However, which gene(s) is causal, how the risk genetic or epigenetic factors alter gene expression, and how they fit into pathology and syndrome pathways [119]. New drugs for SCZ are

essential needs for the patients. These drugs have to target pathophysiological alterations that are specific to syndrome. Schizophrenia is a multifactorial and strongly biologically heterogeneous syndrome. Identification of homogenous subgroups is increasingly necessary for new drugs discovery [120]. So, the above mentioned assays will help the researchers to understand the pathological processes and the development of better treatments [15, 119].

In addition to different approaches to the analysis for genes associated with SCZ, the genetics and epigenetic of specific psychopathology, including cognitive impairments, negative signs, disorganized behaviors, etc., need to be addressed. In this regard, neuroimaging genetics approach will be useful. In addition, a psychiatric translational and phenomics approach (genome to mind phenome), understanding the pathology of syndrome in different levels, such as genetics, epigenetic, proteomics, and other omics data, and also neural circuit abnormalities, and endophenotypes related to psychopathology and clinical phenotypes are another essential steps.

6. Conclusion

Schizophrenia is a complex, heterogeneous, and multifactorial syndrome. It has many levels, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, neural circuit, endophenotype, and albeit clinical presentations. It seems that an ideal "multi-level diagnostic system" has to include all of these levels to make a bioprofile. By doing this in the near future, we hope to have a more reliable and valid diagnostic system, better approach to its treatment and also prevention of mental disorders, including SCZ.

Conflict of interest

The author declares to have no conflicts of interest.

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Chapter 7

Immune System Dysregulation and Autoimmunity in Schizophrenia: IgGs from Sera of Patients with Several Catalytic Activities

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73194

Abstract

Schizophrenia is usually a progressive mental illness with very different polymorphic symptoms. Several different theories of schizophrenia were discussed; the causes of this disease are not yet clear. Destruction of DNA, RNA, and myelin basic protein (MBP) by inflammation caused by autoimmune reactions has been revealed. Healthy humans usually do not develop abzymes. It was shown that DNase, RNase, and MBP-hydrolyzing abzymes are easily detectable at the beginning of different autoimmune diseases (AIDs). During the development of spontaneous and induced AIDs in mice, a specific reorganization of their immune system associated with the generation of abzymes hydrolyzing different autoantigens was revealed. SCZ is currently not assigned to classical autoimmune diseases. However, the sera of approximately 30% of SCZ patients demonstrated a high level of anti-DNA Abs (comparing to 37% of SLE patients); abzymes hydrolyzing DNA, RNA, and MBP were revealed in 80–100% of SCZ patients. The site-specific hydrolysis of four known SCZ-specific microRNA playing an important role in the regulation of several genes functioning was revealed. Anti-MBP IgGs hydrolyze specifically only MBP but not other proteins. The data indicate that SCZ patients may to a certain extent show similar to SLE and MS patients' typical signs of autoimmune processes.

Keywords: schizophrenia, autoimmunity, catalytic antibodies, hydrolysis of autoantigens

1. Introduction

Schizophrenia (SCZ) is a highly heritable brain disorder, and it is one of the most relevant problems of psychiatry [1]. The prevalence of SCZ in the human population is approximately 1%, and this disease is the most severe mental diseases [2]. Schizophrenia is a progressive mental illness demonstrating polymorphic symptomatology and resulting in the persistent violation of social adaptation and ability to work. In SCZ, a violation of synaptic transmission resulting in neuronal damage and severe dysfunction was observed [3–5]. These changes often may begin to arise in utero or early childhood [6, 7].

Several different theories of SCZ were discussed, but all of them cannot be definitively concluded for or against the degenerative or neurodevelopmental hypothesis and did not provide clarity concerning the mechanism of schizophrenia development [8].

The dopamine hypothesis of schizophrenia is a model, attributing symptoms of SCZ to a disturbed and hyperactive dopaminergic signal transduction. Since dysfunction of the glutamatergic system is a widely known fact in SCZ [9–12], it is possible that misbalance of dopamine-glutamate homeostasis can lead to the patient's development of generalized oxidative stress [13, 14]. The known theory, however, does not posit dopamine overabundance as a complete explanation of SCZ. Rather, the overactivation of D2 receptors, specifically, is one effect of the global chemical synaptic dysregulation observed in this disorder.

Detection of neurotropic effect which was postulated is associated with the damages of cell membranes [15, 16]. It is believed that the brain cell membranes damage causes the formation of autoantigens and as the consequence autoantibodies (Abs) [17–19]. Interestingly, Abs to glutamate receptors were revealed in SCZ and many other diseases including typical autoimmune ones [20]. Anti-NMDA-NR1, anti-AMPA-GluR3, anti-NMDA-NR2A/B, and anti-mGluR1 or anti-mGluR5 antibodies were found in subpopulations of patients not only with SCZ but also with encephalitis, epilepsy, SLE, neuropsychiatric SLE, cerebellar ataxia, Sjogren's syndrome, and mania or stroke [20]. These autoimmune Abs against anti-glutamate receptors can bind neurons in few brain regions, activate receptors of glutamate, decrease glutamate receptor's expression, activate blood-brain barrier endothelial cells, damage the brain, impair glutamate-induced signaling and function, kill neurons, and induce psychiatric/behavioral/cognitive abnormalities [20]. The association between SCZ and various inflammatory-autoimmune diseases was reported in several epidemiological surveys. Several studies demonstrated that individuals with SCZ are somehow less likely to have rheumatoid arthritis [21]. Some other autoimmune (AI) disorders have also been linked to schizophrenia, particularly Hashimoto's thyroiditis and celiac disease [22, 23].

During the last decade, new data about increasing recognition of central nervous system (CNS) syndromes associated with autoimmune processes leading to the production of autoantibodies to CNS cell surface antigens were obtained [24]. Most of these syndromes present outstanding mental and cognitive symptoms, among the variety of neurological manifestations such as seizures, movement disorders, and autonomic dysfunction, and is best described as "autoimmune encephalopathy."

The causes of schizophrenia include environmental and genetic factors [25]. Recently, a genome-wide microarray study in postmortem brains of SCZ patients has explored expression profiling of immune-modulatory genes [26]. Genetic factors in SCZ include a variety of common and rare genetic variants [27]. It was shown that SCZ is a multifactorial disease, the pathogenesis of which can contribute to numerous genes and the products of their transcription [28]. Therefore, in research of schizophrenia pathogenesis, understanding a possible role of microRNAs may be important. Short non-coding microRNAs (18–25 nucleotides) can individually regulate up to several hundred genes. Disturbances in microRNA (microRNA-regulated gene network) lead to alteration in the expression of many genes. The expression of different microRNAs in plasma [29, 30], mononuclear cells of peripheral blood [31] as well as in various brain regions [32, 33] in patients with SCZ was detected. In addition, genome-wide association study shows, in SCZ, a close association of a single-nucleotide polymorphism of miR-137 and miR-9-5p [34–36]. MicroRNA miR-137 plays an important role in the differentiation of embryonic stem cells, proliferation, and differentiation of neurons, the maturation of the synapses [37]. The miR-137 inhibits AMPA receptor-mediated synaptic transmission by decreasing the expression of the GluA1 subunit of this receptor [38]; influences the release of neurotransmitters from synaptic vesicles and disrupts synaptic plasticity [39]. Interestingly, one of the genes regulating the expression of miR-137, is a protein zinc finger 804A (zinc finger protein 804 A-ZNF804A), which in turn inhibits the expression of catechol-O-methyltransferase (catechol-O-methyltransferase), and D2 receptor of dopamine [37], which leads to a disruption in dopamine neurotransmission. In the regulation of expression of the D2 receptor of dopamine is also involved in the miR-9-5p [36]. It is shown that miR-9-5p is involved in neuronal migration and that the expression of miR-9-5p in patients with schizophrenia is reduced in neuronal cells precursors (neural progenitor cells) [40]. It was also found that miR-219 plays an important role in the differentiation of oligodendrocytes and myelination of axons of neuronal cells [41].

It is known that enzymes can play important role in the pathogenesis of different diseases: dysfunction of enzymes systems involved in the metabolism of biogenic amines (indolamine, catecholamines) during mental disorders including SCZ [23, 42].

The above data testify to the fact that some patients with SCZ are clearly showing signs of typical autoimmune pathologies. However, the importance of immunological changes resulting in the loss of the tolerance to self-antigens in the pathogenesis of SCZ is currently not accepted. Summarizing all existing hypotheses, one can say that SCZ is a very multifactorial disease including some variations in the functioning of neurotransmitter systems associated with the changes in the rate of synthesis or breakdown of the neurotransmitter, possible modifications of the structure of the relevant receptors, genetic predisposition and a dysregulation between the immune and nervous systems, important role of genetic factors and microRNAs, as well as enzymatic systems.

Despite the fact that SCZ is not currently attributed to typical autoimmune diseases, the immune system and dysregulation of immune cells, including autoimmune processes in this disease, are not to be excluded [17–20, 24]. Schizophrenia, autoimmunity and immune system dysregulation are reviewed in [43, 44]. Thus, the search of the importance of different mechanisms of SCZ development including possible autoimmune factors is undoubtedly actual. In this

connection, some literature data should be mentioned. Catalytically active artificial antibodies or abzymes (Abzs) against transition chemical reaction states were well studied (reviewed in [45–47]). In the last three decades, it was shown that auto-antibodies from the blood of patients with different AIDs can possess enzymatic activities and that their occurrence is a specific feature of these pathologies (reviewed in [47–53]). Similarly to artificial Abzs to transition states of chemical reactions [45–47], natural abzymes are Abs raised directly against enzyme substrates acting as haptens of proteins mimicking transition states of catalytic reactions. In addition, anti-idiotypic Abs against catalytic centers of enzymes can be induced in AIDs, and they also possess catalytic activities [47–56].

Even in the sera of healthy mammals, auto-antibodies to different peptides, proteins, DNA, and RNA are detectable, and their titers vary significantly [47–57]. The sera of SLE patients usually contain DNA and anti-DNA Abs in increased concentrations, and SLE is usually considered to be associated with the autoimmunization of patients with DNA. However, the sera of patients with several different autoimmune diseases contain DNA and anti-DNA Abs [57], as well as RNA and anti-RNA Abs in high concentrations [58–61]. Many anti-DNA Abs are directed against histone-DNA nucleosomal complexes appearing from internucleosomal cleavage during apoptosis [62].

Despite the fact that the blood of healthy donors usually contains autoantibodies to DNA, RNA, and many different proteins, these Abs usually do not possess catalytic activities [47–56]. It was shown, that in the case of different autoimmune patients, experimental mice abzymes with DNase, protease, and amylase activities are the earliest and statistically significant markers of autoimmune pathology onset and following development [63–69]. Enzymatic activities of Abs are detectable even at the stage of pre-disease when there is no visible markers of autoimmune diseases and changes in proteinuria, and the anti-antigen titers including DNA and proteins are within the typical ranges of these indicators for healthy humans and experimental mice [63–69]. Therefore, a detectable level of Ab activities can be considered as valuable index even at the beginning of the pathology (pre-disease) and obvious pathology conditions of spontaneous or induced autoimmune diseases [63–69].

Natural polyclonal IgGs and/or IgAs and IgMs hydrolyzing mononucleotides, DNA, RNA, oligopeptides, proteins, and polysaccharides, from the sera of patients with several AIDs and several viral diseases with significant autoimmune reactions were revealed (reviewed in [47–56]). Bence-Jones proteins of multiple myeloma patients [70], DNase abzymes from SLE [71] and MS [51] are cytotoxic, induce nuclear DNA fragmentation and cause cell death by apoptosis, leading to increase in the concentration of many different cell components including DNA, RNA, and proteins in patients with various AIDS. Abzymes with RNase activity in autoimmune diseases are of particular interest. The same polyclonal preparations of Abzs hydrolyzed RNA approximately 10-fold to 300-fold faster than DNA [72–74].

It has been recently shown that myelin basic protein (MBP)-hydrolyzing activity is an intrinsic property of IgGs of SLE patients [75–78] as well as IgGs, IgMs, and IgAs from the sera of MS patients [79–82]. In MS and SLE, anti-MBP abzymes with protease activity can attack MBP of the myelin-proteolipid sheath of axons and can play an important harmful role in MS and SLE pathogenesis [75–82].

In this review, an analysis of the catalytic activities of currently described abzymes in the blood of patients with SCZ was carried out. These abzymes of SCZ with different catalytic activities are compared with other Abzs in AIDs. In addition, a possible role of defects of immune systems leading to the production of abzymes is discussed.

Taking into accoIn this review, an analysis of the catalytic activities of currently described abzymes in the blood of patients with SCZ. These abzymes of SCZ with different catalytic activities are compared with other Abzs in AIDs. In addition, a possible role of defects of immune systems leading to the production of abzymes is discussed.unt the ability of autoimmune patient's abzymes to hydrolyze RNA together with the important role of microRNAs in proliferation, differentiation, and maturation of neuronal cells and the relationship of microRNAs with the development of SCZ, the aim of present chapter was to analyze the RNA-hydrolyzing activity of Abs of schizophrenia patients. In addition, we have described substrate specificity antibodies in the hydrolysis of specific for schizophrenia microRNA.

As mentioned above, schizophrenia is not attributed to the classic autoimmune diseases. At the same time, it was recently shown that the sera of ~30% of SCZ patients showed a higher content of anti-DNA Abs (comparing to 37% of SLE patients), while DNase abzymes were revealed in 80% of SCZ patients [83]. In addition, it was shown that abzymes hydrolyzing MBP were revealed in 82% of the SC patients. These data can indicate for at least a pronounced autoimmune component in patients with SCZ. Interestingly, the researchers of the London medical Institute Oliver House advanced theory, according to which schizophrenia is the result of a lesion of immune system of the brain (http://the-newspapers.com/2017/11/08/schizophrenia-has-announced-a-disease-of-the-immune-system).

2. Abzymes with DNase activity

The generation of auto-Abs to DNA usually occurs not only in patients with AI, viral, and bacterial diseases but also in healthy humans [23, 24, 32–35, 55]. We have compared the relative levels of Abs interacting with DNA in sera of 20 SCZ patients and 20 healthy donors. The levels of Abs interacting with single-stranded (ss) DNA (A_{450}/ml) for 20 healthy donors were detectable; they varied from 0.07 to 0.14 specific units (average value—0.13 ± 0.02) and, on average, they were 1.3-fold higher ($P = 6.3 \times 10^{-4}$) than those interacting with double-stranded (ds) DNA varying from 0.1 to 0.18 (0.1 ± 0.02) [83, 84]. The average level of Abs (A_{450}/ml) for the total group of patients with SCZ interacting with ssDNA (range from 0.1 to 1.4; average value 0.23 ± 0.13) was only 1.1-fold lower ($P = 6.9 \times 10^{-4}$) than that for interacting with dsDNA (range from 0.15 to 0.44; average value 0.25 ± 0.07). The average level of Abs interacting with dsDNA for healthy donors is 2.5-fold lower ($P = 1.0 \times 10^{-6}$) than that for SCZ patients, while for antibodies interacting with ssDNA, it is lower only 1.8-fold ($P = 0.05$). Several SCZ patients are characterized by very high levels of Abs interacting with ssDNA and dsDNA (0.31–1.4 A_{450}/ml) characterizing patients with SLE (0.51 ± 0.50 and 0.66 ± 0.48 A_{450}/ml, respectively) and with MS (0.22 ± 0.18 and 0.39 ± 0.26 A_{450}/ml, respectively) [53–56].

The average relative level of Abs interacting with dsDNA (0.23 ± 0.05 A_{450}/ml) for SCZ patients with positive symptoms was 1.2-fold lower than that for patients with negative symptoms

(0.28 ± 0.07 A_{450}/ml) (**Table 2**). At the same time, the average level of Abs interacting with ssDNA (0.3 ± 0.22 A_{450}/ml) for patients with positive symptoms was 1.9-fold higher than that for SCZ patients demonstrating negative symptoms (0.16 ± 0.07 A_{450}/ml). It was accepted that increased concentration of anti-DNA Abs is a characteristic of patients with SLE. However, concentration of anti-DNA Abs compared with healthy donors is higher in patients with SLE (37% of patients), MS (17–18%), Sjogren's syndrome (18%), Hashimoto thyroiditis (23%), rheumatoid arthritis (7% of patients), and myasthenia gravis (6%) [57]. Overall, ~30% of SCZ patients (comparable with SLE patients 37% [57]) displayed higher content of Abs interacting with ss- and dsDNA when compared to healthy donors.

As mentioned above, polyclonal natural DNA-hydrolyzing IgGs and/or IgAs and IgMs were revealed in blood sera of patients with several AI and viral diseases (reviewed in [47–57]). Electrophoretically and immunologically homogeneous IgGs were obtained from the sera of 20 SCZ patients and 20 healthy volunteers by sequential chromatography of the serum proteins on Protein A-Sepharose using conditions providing removing non-specifically bound proteins, followed by FPLC gel filtration in an acidic buffer destroying immune complexes as in [75–81]. For some experiments, equimolar mixtures of 20 IgG preparations of SCZ patients (scz-IgG_{mix}) and 20 preparations of healthy donors (healthy-IgG_{mix}) were used [83]. To show that IgGs of SCZ patients possess DNase activity, we have checked several known strict criteria [52–56, 85]. The following main criteria were used [83]: (a) Abs should be electrophoretically homogeneous (**Figure 1A**); (b) Abs after gel filtration in an acidic buffer (pH 2.6) dissociating strong noncovalent complexes IgGs must possess DNase activity and the peak of the activity should tracked exactly with the intact Abs (**Figure 1B**); (c) immobilized polyclonal antibodies against the human Abs should completely absorb the DNase activity; (d) among criteria, there is an hardest one; if it is carried out, all other criteria are also met. To exclude any possible artifacts due to hypothetical traces of contaminating canonical DNases, scz-IgG_{mix} preparation was subjected to SDS-PAGE in a gel containing polymeric DNA, and its DNase activity was analyzed after gel incubation in the standard reaction buffer (**Figure 1C**). Ethidium bromide staining of the gels revealed sharp dark bands against a fluorescent DNA background only in the position of intact IgG_{mix} before (lane 3) and only in the position of light chains after Abs reduction with DTT (lane 4). There was no revealed DNase activity of healthy-IgG_{mix} before (lane 5) and after Abs reduction with DTT (lane 6).

The intact IgGs have molecular masses (~150 kDa) significantly higher than for all canonical human DNases (35–36 kDa), while DNases have higher molecular masses than light chains of IgGs (22–25 kDa). SDS usually dissociates all protein complexes. The detection of DNase activity only in the gel zones of intact IgGs and their light chains as well as the absence of any other activity and protein bands (**Figure 1C**) ensure direct evidence that SCZ IgGs hydrolyze DNA and are not contaminated with canonical DNases. Several other strict criteria were also fulfilled (see below).

We have shown that the DNase activity of IgGs purified by chromatography on Protein G-Sepharose followed by FPLC gel filtration can be used for the evaluation of their relative activity (RA) without additional purification. The RAs of SCZ patients IgGs were significantly varied from patient to patient. However, 16 of 20 samples (80%) had high or detectable DNase activity. The distributions of the RAs for IgGs of different SCZ patients with positive and

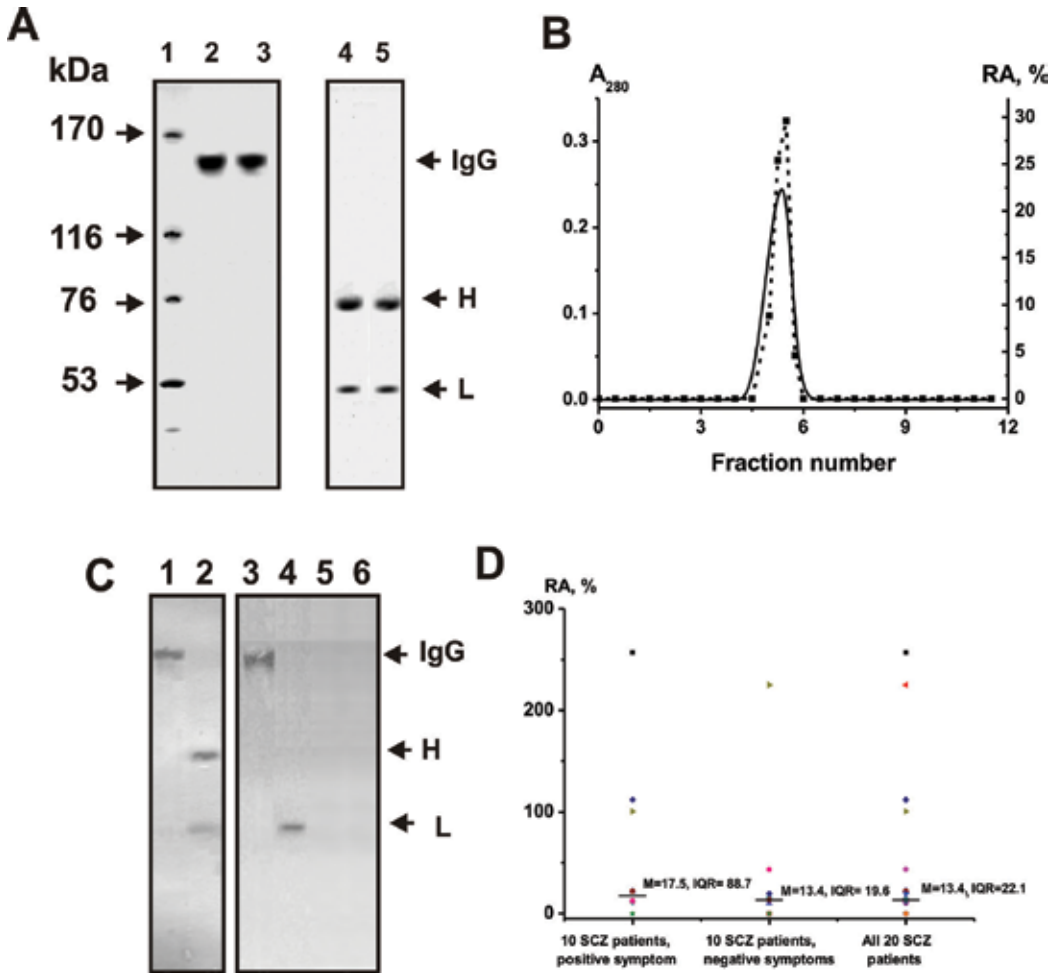

Figure 1. SDS-PAGE analysis of IgG_{mix} (7 μg) corresponding to the mixtures of scz-IgG_{mix} (lane 2) from the sera of 20 patients with SCZ and healthy-IgG_{mix} (lane 3) corresponding to 20 healthy donors in a nonreducing 3–16% gradient gel or in a reducing 12% gel (lanes 4 and 5, respectively) followed by silver staining (A); the lane 1 arrows indicate the positions of molecular mass markers. The application of the strict criteria is to prove that the DNase activity of Abs is the intrinsic property of scz-IgG_{mix}. FPLC gel filtration of scz-IgG_{mix} on a Superdex 200 column using an acidic buffer (pH 2.6) after IgGs pre-incubation in the same buffer (B): (■), relative activity (RA, %) of IgGs in the hydrolysis of supercoiled DNA; (—), absorbance at 280 nm (A280). A complete hydrolysis of 18 μg/ml scDNA for 2 h was taken for 100%. The initial rate determination error from three experiments in each case did not exceed 7–10%. Assay of DNase activity of scz-IgG_{mix} from schizophrenia patients in-gel containing thymus DNA before (lane 3) and after IgGs reduction with DTT (lane 4); lane 5 corresponds to healthy-IgGmix before treatment with DTT (C). DNase activity was revealed after gel staining with ethidium bromide as a dark band on the fluorescent background. There was no revealed catalytic activity of healthy-IgG_{mix} before its reduction (lane 5). A part of the used gel was stained with Coomassie R250 to find the position of intact scz-IgG_{mix} before (lane 1) as well as its free heavy and light chains after Ab reduction (lane 2). The distribution of the RAs (in the hydrolysis of scDNA) corresponding to SCZ patients with positive and negative symptoms within different ranges (D). The median (M; solid lines) and interquartile ranges (IQR) were estimated using the Mann-Whitney test.

negative symptoms are shown in **Figure 1D**. Finally, to compare RAs of DNase IgGs of SCZ patients with those for patients with other diseases, the values of apparent k_{cat} in the hydrolysis of DNA for every IgG preparation (k_{cat} = V (M/min)/ [IgGs] (M) and average values of parameters were calculated (**Table 1**) [83].

One of the criteria of Abs' activity is their higher affinity for substrates comparing with canonical DNases. The K_m and k_{cat} values for scDNA hydrolysis were estimated. First, IgG-19 corresponds to the patient with negative symptoms (NS) of SCZ, while IgG-1 and IgG-6 to patients with positive symptoms (**Table 1**). The K_m value for IgG-19 (K_m = 95 ± 18 nM) was comparable with that for IgG-1 (K_m = 85.0 ± 12.0 nM) and IgG-6 (K_m = 80.0 ± 12.0 nM), while k_{cat} for IgG-19 ((2.7 ± 0.3) × 10^{-3} min^{-1}) and IgG-6 ((3.0 ± 0.3) × 10^{-3} min^{-1}) were comparable, but lower than that for IgG-1 ((7.9 ± 0.5) × 10^{-3} min^{-1}). Thus, the affinity of scDNA for SCZ IgGs was in the range 80–95 nM, which corresponds to typical K_d (and K_m) values for interactions of antibodies with antigens; it is approximately 3–4 orders of magnitude higher than affinity of DNase I for scDNA (K_m = 46–58 μM) [86].

Number of patients (sex)	**Abs to dsDNA, A_{450}/ml**	**Abs to ssDNA, A_{450}/ml**	**Relative hydrolysis of DNA, %**	**k_{cat} ×10^5,min^{-1}**
	1	**2**	**3**	**4**
	Positive symptoms (PS)			
1 (M)	0.35	1.4	257$^{\mu}$	39.6***
2 (M)	0.19	0.11	11.7	1.8
3 (M)	0.2	0.31	22.2	3.4
4 (M)	0.19	0.16	11	1.7
5 (M)	0.24	0.19	12	1.9
6 (M)	0.15	0.11	100.4	15.5
7 (M)	0.21	0.14	112	17.3
8 (F)	0.2	0.23	22	3.4
9 (F)	0.34	0.25	13	2.0
10 (F)	0.18	0.11	0	0
Average (PS)	0.23±0.05	0.30±0.22	56.1±60.2	8.7±9.3
M (IQR) (PS)ϒ	0.20 (0.05)	0.18 (0.14)	17.5 (88.7)	2.7 (13.7)
Correl. coeff. (PS)	Groups 1–2 (0.71)		1–3 (0.46)	2–3 (0.84)
Negative symptoms (NS)				
11 (M)	0.48	0.23	0$^{\mu}$	0
12 (M)	0.28	0.2	0	0
13 (M)	0.21	0.13	10.4	1.6
14 (M)	0.22	0.16	15.0	2.3
15 (M)	0.23	0.1	13.3	2.1
16 (F)	0.44	0.12	225	34.7
17 (F)	0.24	0.11	19.6	3.0
18 (F)	0.17	0.19	13.6	2.1
19 (F)	0.25	0.16	43.4	6.7

Number of patients (sex)	Abs to dsDNA, A_{450}/ml	Abs to ssDNA, A_{450}/ml	Relative hydrolysis of DNA, %	k_{cat} ×10^5,min^{-1}
	1	2	3	4
	Positive symptoms (PS)			
20 (F)	0.24	0.15	0	0
Average (NS)**	0.28±0.07	0.16±0.03	34.0±40.1	5.3±6.2
M (IQR) (NS)	0.24 (0.06)	0.16 (0.07)	13.4 (19.6)	2.1 (3.0)
Average, total group	0.25±0.07	0.23±0.13	45.1±50.4	7.0 (7.9)
M (IQR), total group$^{\Upsilon}$	0.23 (0.07)	0.16±0.1	13.4 (22.1)	2.1 (3.4)
Correl. coeff. (NS)	1–2 (0.3)	1–3 (0.5)	2–3 (0.35)	
Correl. coeff., complete group	1–2 (0.3)	1–3 (0.4)	2–3 (0.62)	

*For each value, a mean of three measurements is reported; the error of the determination of values did not exceed 7–10%.

**Average values are reported as mean ± S.E; they were recalculated to standard conditions and complete hydrolysis of 18 μg/ml scDNA after 1 h of incubation in the presence of 0.1 mg/ml IgG was taken for 100%.

***The average apparent k_{cat} values of the reaction of DNA hydrolysis were calculated using average RA values: k_{cat} = V (M/min)/ [IgGs] (M), 18 μg/ml scDNA was used.

μStatistical significance of differences in DNase activity between schizophrenia patients with positive and negative symptoms (P = 0.026).

ΥThe median (M) and interquartile ranges (IQR) were calculated using the Mann-Whitney test.

Table 1. The relative concentration of fnti-DNA Abs, RAs (%), and the apparent k_{cat} values characterizing hydrolysis of scDNA by IgGs from the sera of SCZ patients.*

3. Abzymes with RNase activity

It was shown in several articles that IgGs from the sera of healthy humans cannot hydrolyze RNA [87–90]. At the same time, IgGs from the sera of patients with SLE, MS, Hashimoto's thyroiditis and some other autoimmune pathologies effectively hydrolyze different ribopolynucleotides and tRNAs [87–90].

Electrophoretically and immunologically homogeneous IgGs purified from the sera of 35 SCZ patients according to [75–83] as described above were used [91]. On the first step, we used a mixture of equal amounts of 35 polyclonal IgGs (scz-IgG_{mix}) and 15 healthy donors. Then, we checked the fulfillment of the strict criteria described above. The homogeneity of the typical 150-kDa IgG_{mix} was confirmed by SDS-PAGE with silver staining similar to **Figure 1**. The activity peak of the IgG_{mix} treated with acidic buffer (pH 2.6) coincided under gel filtration exactly with the peak of intact Abs (**Figure 2A**) Immobilized polyclonal mouse IgGs against the light chains of human IgGs completely bind the RNase activity. Scz-IgG_{mix} was subjected to SDS-PAGE in a gel co-polymerized with polymeric yeast RNA, and its RNase activity was revealed after the gel incubation in the standard reaction buffer only in the position of intact scz-IgG_{mix}. (**Figure 2B**). Canonical human RNases have significantly lower molecular masses (13–15 kDa) than the intact IgGs (150 kDa). Therefore, the activity detection in the gel zones

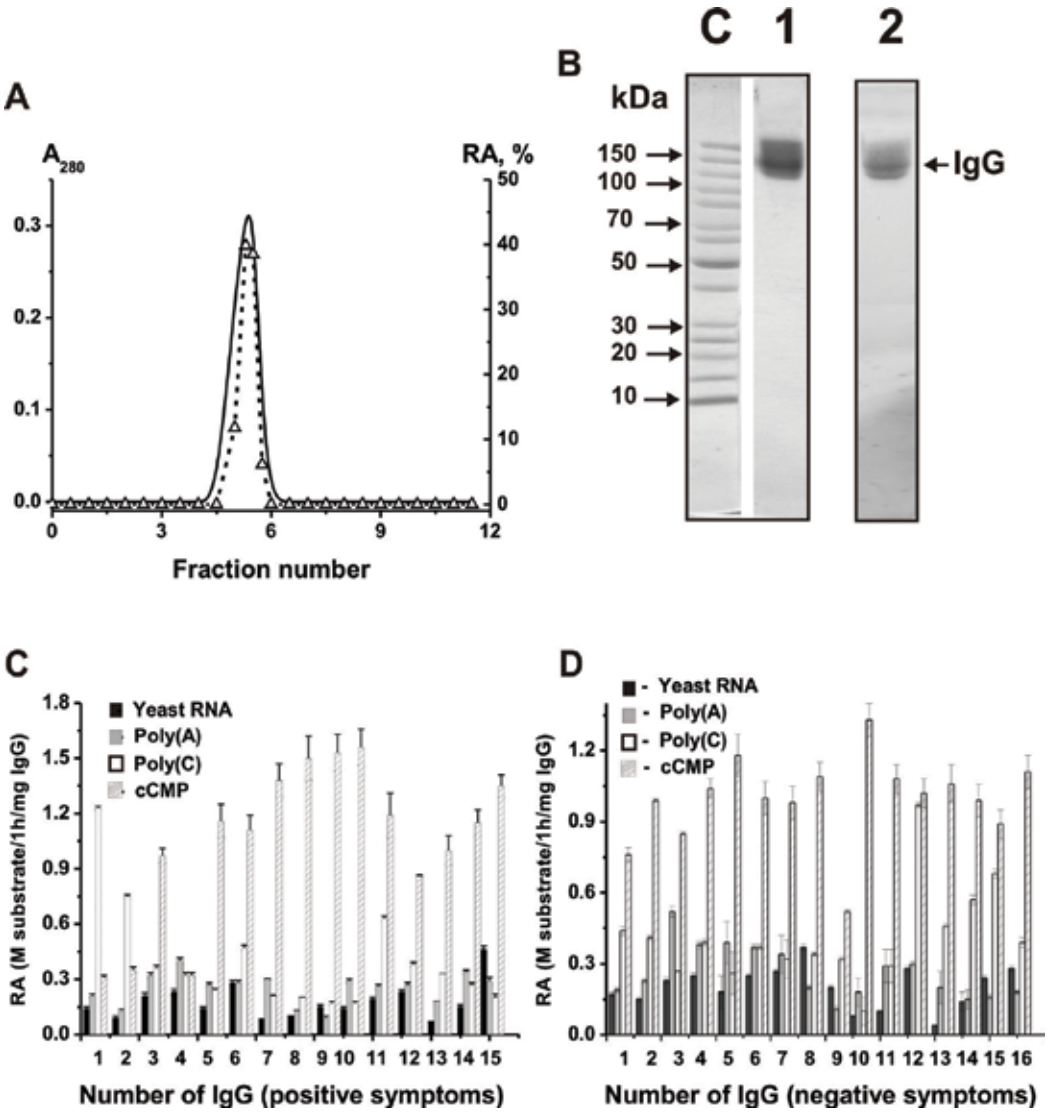

Figure 2. Verification of the strict criteria to prove that the RNase activity of IgGs is an intrinsic property of IgG_{mix}. FPLC gel filtration of scz-IgG_{mix} on a Superdex 200 column equilibrated with an acidic buffer (pH 2.6) after its pre-incubation in the same buffer (A): (—), absorbance at 280 nm (A_{280}); (Δ), relative activity (RA, %) of IgG_{mix} in the cleavage of RNA. A complete hydrolysis of poly(C) for 7 h was taken for 100%. The error in the initial rate estimation from two experiments in each case did not exceed 7–10%. Assay of RNase activity of scz-IgG_{mix} in-gel containing polymeric yeast RNA (lane 2). RNase activity was detected after gel staining with ethidium bromide as a dark band on the fluorescent background. A gel part was stained with Coomassie R250 to show the position of intact scz-IgG_{mix} (lane 1). Lane C corresponds to molecular mass markers. Relative activity of individual IgGs of patients with positive (C) and negative (D) symptoms of SCZ in the hydrolysis of yeast RNA, poly(A), poly(C), and cCMP.

of only intact scz-IgG_{mix} together with the absence of any other activity and protein bands (**Figure 2B**) guarantee direct evidence that schizophrenia IgGs cleave RNA and IgGs are not contaminated by canonical RNases. Several other strict criteria were also fulfilled (see below).

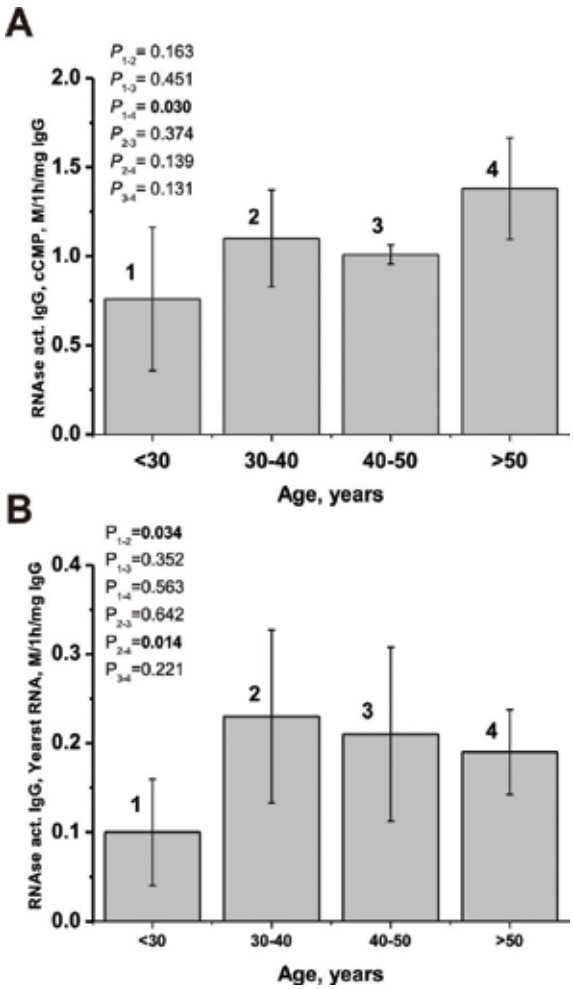

Figure 3. Dependencies of average activities of IgGs of four groups of SCZ patients with different age in the hydrolysis of cCMP (A) and poly(C) (B).

The relative activities of IgGs significantly varied from patient to patient. However, all 15 samples of patients with positive and 16 ones with negative symptoms of SCZ demonstrated detectable or high RNase activity (**Figure 2C** and **D**). The relative average activity for patients with SCZ positive symptoms varied essentially (M/1 h/mg IgG): cCMP (0.31–1.56; average value (AV) = 1.05 ± 0.43), poly(C) (0.17–1.23 AV = 0.4 ± 0.29), poly(A) (0.09–0.4; AV = 0.25 ± 0.09), and yeast total RNA (0.08–0.46 AV = 0.18 ± 0.1) (**Figure 2C**). Similar situation was observed for patients with negative symptoms (M/1 h/mg IgG): cCMP (0.52–1.18; AV = 0.99 ± 0.18), poly(C) (0.1–0.68, AV = 0.41 ± 0.2), poly(A) (0.11–0.52; AV = 0.20 ± 0.11), and yeast total RNA (0.4–3.1 AV = 1.68 ± 0.71) (**Figure 2D**). The difference in average activities of IgGs from patients with positive and negative symptoms was very small: cCMP (1.1-fold), poly(C) (1.03-fold), poly(A) (1.3-fold), and yeast total RNA (1.1-fold). According to non-parametric Kruskal-Wallis analysis,

in none of these cases, there was a statistically significant difference ($P > 0.2$). Interestingly, a clear correlation of the RNase RAs with the duration of SCZ was not observed ($P = -0.015 \pm 0.14$) except with activity of IgGs in poly(C) hydrolysis (+ 0.47). The tendency of increase in activity of IgGs in the hydrolysis of cCMP and poly(C) with age of SCZ patients was revealed (**Figure 3**). A statistically significant difference in the mean values of the relative activity in the case of cCMP hydrolysis was observed for a group of patients younger than 30 and over 50 years old ($P = 0.03$) (**Figure 3A**). For activity in poly(C) hydrolysis, statistically significant difference was revealed between the groups younger 30 and 30–40 ($P = 0.034$) as well as group of patients over 50 years old ($P = 0.014$) (**Figure 3B**). In addition, a good statistically significant correlation was observed between the activity in hydrolysis of cCMP (CC = + 0.896) and composite index of SCZ, demonstrating a difference between parameters of positive symptoms and negative symptoms and showing the prevailing symptoms. Interestingly, a moderate but statistically significant negative correlation was observed between the efficiency of poly(C) hydrolysis and PANSS + (or PANSS Positive scale) evaluating signs that are redundant in relation to normal mental status (−0.43).

4. Hydrolysis of microRNAs

As mentioned above, some microRNAs regulate up to several hundred genes in the pathogenesis of SCZ [34–41]. We have analyzed the hydrolysis by SCZ abzymes' four known microRNAs playing an important role in SCZ [91]. **Figures 4–7** demonstrate typical patterns of miR-137, miR-9-5p, miR-219-2-3p, and miR-219a-5p hydrolysis; specific % of the hydrolysis for each IgG and the average percent of microRNAs hydrolysis by 21 different Abs were estimated. Percentage of the microRNA hydrolysis by different IgGs in the same conditions varied and average values decreased in the following order: miR-219a-5p (the range: 7.4–99.7%, AV = 71.0 ± 32.7%) ≥ miR-137 (14.9–99.9%, AV = 66.2 ± 29.2%) ≥ miR-9-5p (3.1–99.9%, AV = 56.7 ± 32.9%) ≥ miR-219a-2-3p (7.4–99.7%, AV = 52.4 ± 34.5%) (**Figures 2–5**). The correlation coefficients between sets of RAs in the hydrolysis of all 4 microRNAs are quite high, 0.84–0.93.

Spatial structures of microRNAs having minimal energy were calculated; **Figure 8A–D** show position of major, moderate, and minor sites of four microRNA hydrolysis by different IgGs (average % of the RNAs hydrolysis by 21 IgG preparations) [91]. One can see that three major sites of microRNAs hydrolysis are located in their loops or duplex parts directly articulated with the loops. The major sites of the hydrolysis of four microRNAs are different, but more often the cleavages occur after or before G-base: miR-219a-5p—6G-7U; 13C-14G, and 8C-9C; miR-137—5 U-6G, 8 U–9 U, and 10A-11A; miR-9-5p—6G-7G, 8 U–9 U, and 13 U-14A; miR-219a-2-3p—5 U-6 U, 8 U-9G, and 13G–14G (**Figure 8**).

We have estimated the K_m and V_{max} (k_{cat}) values for microRNA hydrolysis using different preparations [91]. The dependencies of the initial rate on the microRNA concentration in the reaction catalyzed by IgGs were consistent with Michaelis-Menten kinetics. The K_m and k_{cat} values were to some extent comparable for all microRNAs: miR-137, $K_m = 3.5 \pm 0.2$ μM,

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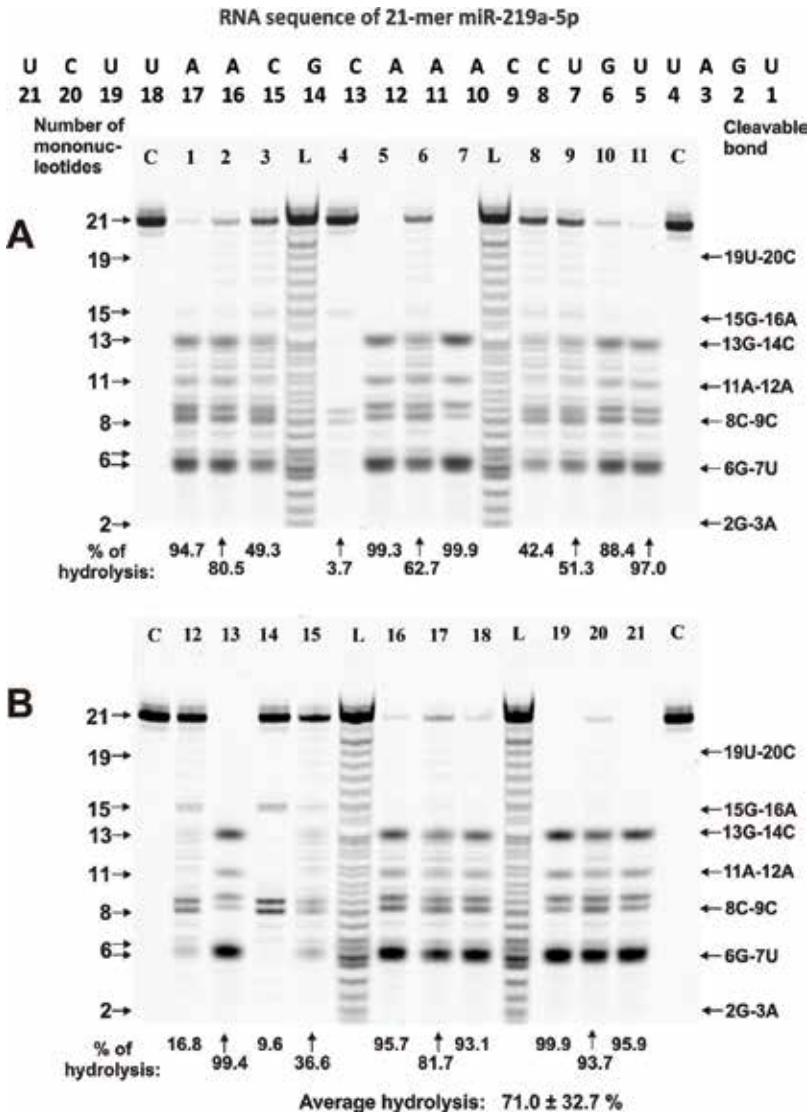

Figure 4. The patterns of flu- miR-219a-5p (0.01 mg/ml) hydrolysis by IgGs (0.1 mg/ml) from sera of 21 SCZ patients. The hydrolysis products were detected by their fluorescence due to the fluorescent residue (flu) on their 5′-ends. The numbers of antibodies, lengths of the products, and the percentage of microRNA hydrolysis by each preparation are indicated in panels A and B.

k_{cat} = 0.14 ± 0.009 min^{-1}; miR-9-5p, K_m = 2.4 ± 0.13 μM, k_{cat} = 0.083 ± 0.003 min^{-1}; miR-219-2-3p. K_m = 1.7 ± 0.12 μM, k_{cat} = 0.10 ± 0.008 min^{-1}; miR-219a-5p K_m = 4.5 ± 0.2 μM, k_{cat} = 0.17 ± 0.02 min^{-1}.

Many anti-DNA Abs are directed against histone-DNA nucleosomal complexes appearing from internucleosomal cleavage during apoptosis [62]. In addition, cell apoptosis leads to the increase in blood the concentration of different nucleases, RNA and its complexes with various

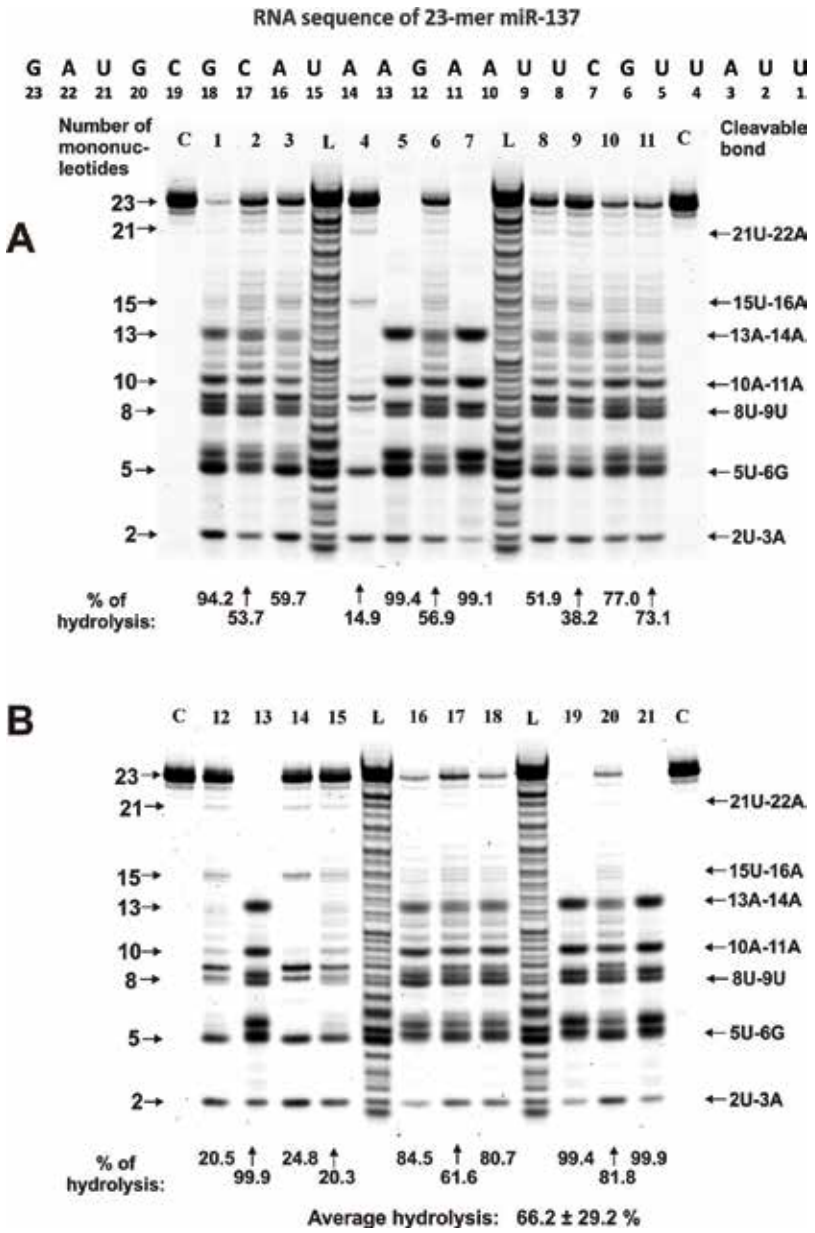

Figure 5. The patterns of Flu-miR-9-5p (0.01 mg/ml) hydrolysis by IgGs (0.1 mg/ml) from sera of 21 different SCZ patients. The hydrolysis products were detected by their fluorescence due to the fluorescent residue (Flu) on their 5′-ends. The numbers of antibodies, lengths of the products, and the percentage of microRNA hydrolysis by each preparation are indicated in panels A and B.

proteins. It was shown that the formation of DNA- and RNA-hydrolyzing Abs occurs after immunization of rabbits with RNA, DNA, DNase I, DNase II, and pancreatic RNase [92–96]. In addition, several monoclonal IgGs against B-DNA of different sequences (from SLE mice) efficiently hydrolyze ss- and dsRNA and DNA in a sequence-independent manner and the

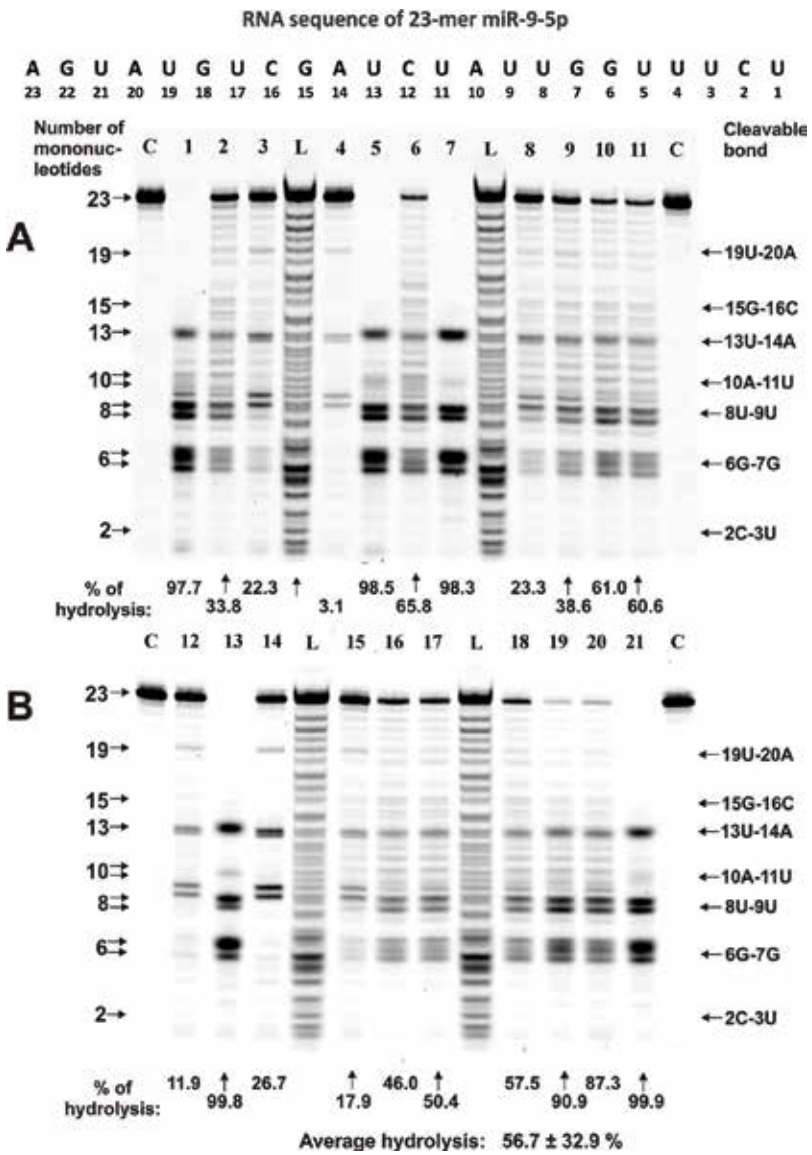

Figure 6. The patterns of Flu-miR-137 (0.01 mg/ml) hydrolysis by IgGs (0.1 mg/ml) from sera of 21 different SCZ patients. The hydrolysis products were detected by their fluorescence due to the fluorescent residue (Flu) on their 5′-ends. The numbers of antibodies, lengths of the products, and the percentage of microRNA hydrolysis by each preparation are indicated in panels A and B.

RNase activity was by a factor of 30–100 higher than that of DNA [97]. Thus, DNase and RNase abzymes can appear in the blood of autoimmune patients due to several very different ways. Since IgGs hydrolyze different homo-polynucleotides and cleavage of four microRNA is site-specific (**Figures 4–8**), one can assume that some sets of RNase abzymes may be specific for some RNAs, while others are not.

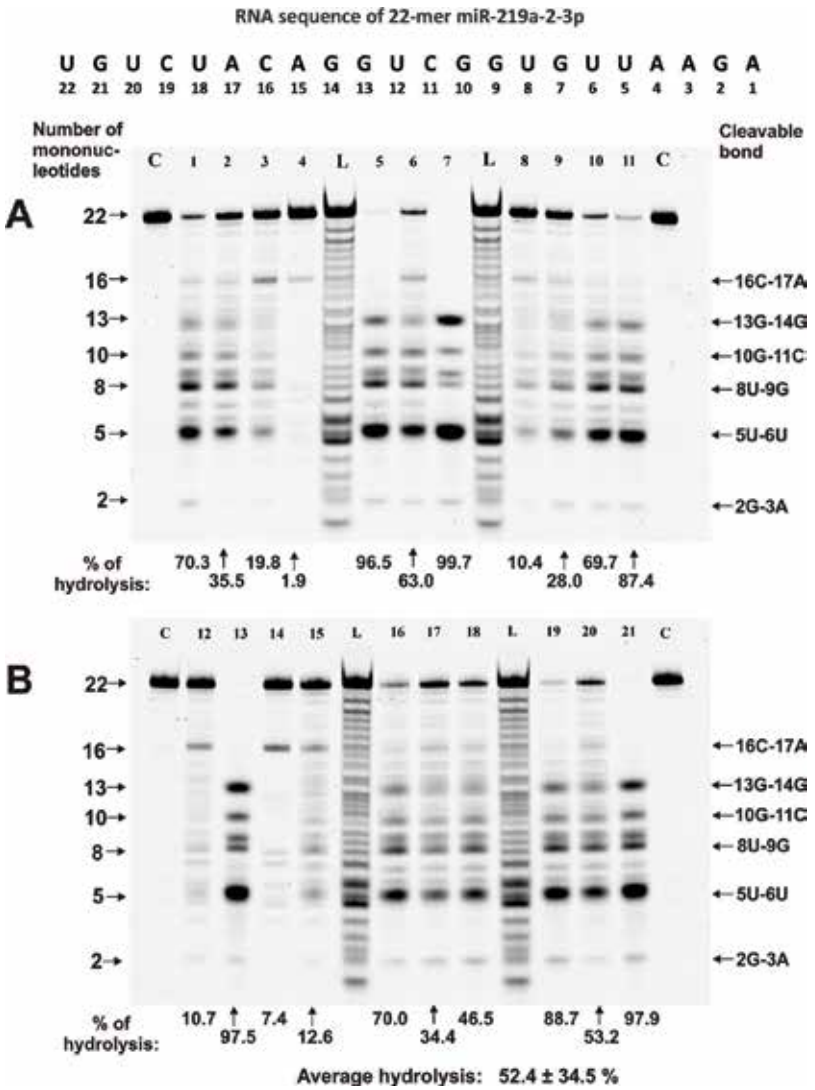

Figure 7. The patterns of Flu-miR-219a-2-3p (0.01 mg/ml) hydrolysis by IgGs (0.1 mg/ml) from sera of 21 different SCZ patients. The hydrolysis products were detected by their fluorescence due to the fluorescent residue (Flu) on their 5′-ends. The numbers of antibodies, lengths of the products, and the percentage of microRNA hydrolysis by each preparation are indicated in panels A and B.

It was shown that 90–95% of Abs SLE and MS patients effectively hydrolyze DNA [47–56]. It was shown that a very high percent IgGs of SCZ patients (80–82%) are active the hydrolysis of DNA [83]. At the same time, similar to SLE and MS [47–56], all 100% schizophrenia IgGs effectively hydrolyze different RNAs [91]. It was shown previously that the appearance of abzymes hydrolyzing DNA and RNA is among the clear and earliest signs of autoimmune reactions [47–56]. In addition, light chains of IgGs from schizophrenia patients are similar to

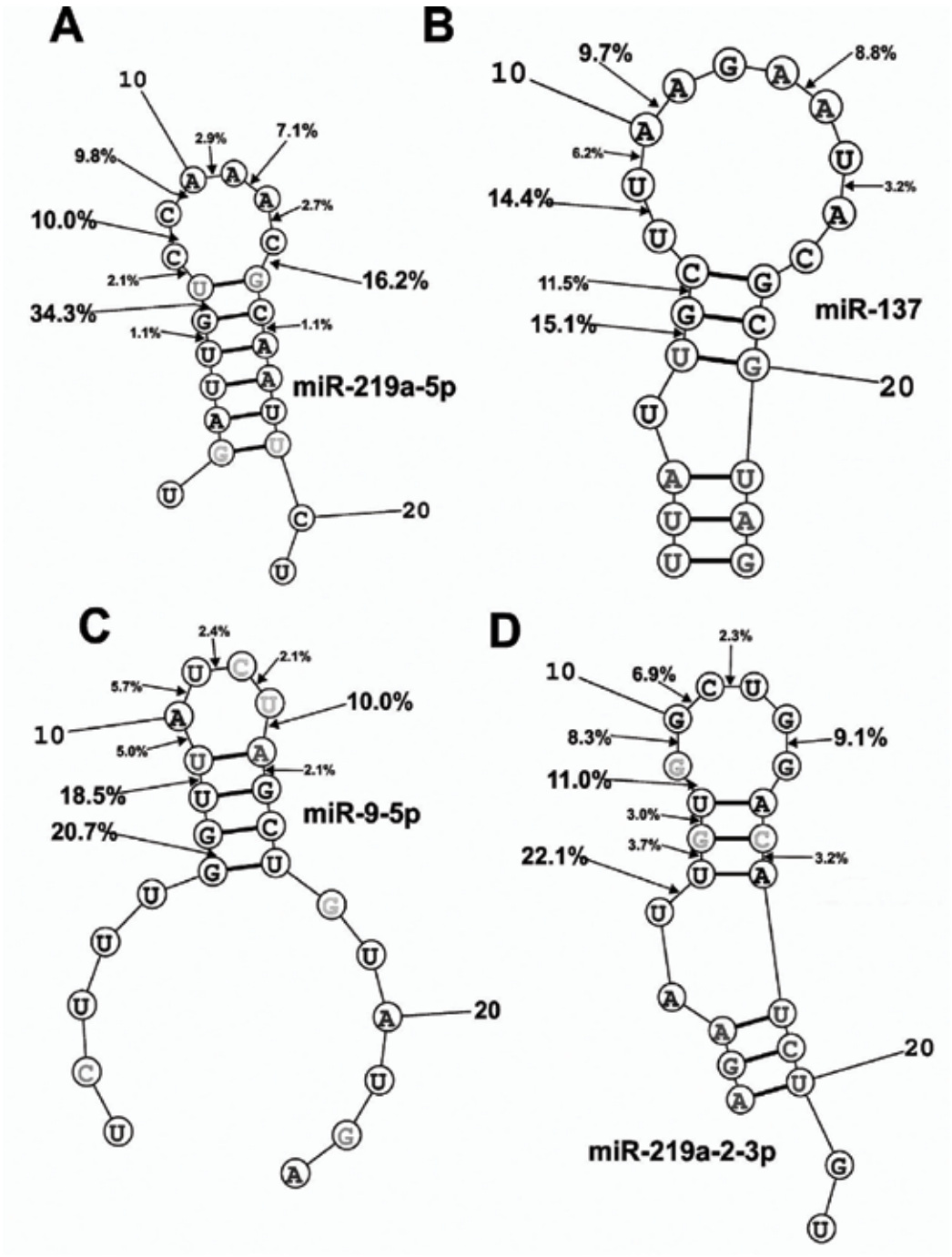

Figure 8. The average efficiency of four micro-RNAs hydrolysis by 21 IgG preparations in all sites of their cleavage (A–D). The position of major and moderate sites of different RNAs hydrolysis is shown.

those of SLE patients, but not to these chains of healthy donors [83]. These data indicate that in patients with SCZ similar to SLE, MS, and other AIDS, there is a trespassing of the immune system leading to the production of abzymes with DNase and RNase activities.

5. Hydrolysis of myelin basic protein

Serum anti-MBP Abs in MS and SLE patients were reported in several articles [75, 76, 79–81, 98, 99]. The relative levels of antibodies against MBP in the sera of 28 patients with SCZ and 15 healthy donors were compared by ELISA (**Table 2**). The concentrations of auto-Abs against MBP for healthy donors were not zero and changed from 0.02 to 0.16 A_{450} units, in average 0.09 ± 0.04 A_{450} units [75, 76, 79–81, 100, 101]. Relative indexes of anti-MBP Abs for 28 SCZ patients varied from 0.04 to 0.26 A_{450} units, in average 0.16 ± 0.068 A_{450} units. For patients with positive symptoms of SCZ, average value (0.18 ± 0.066 A_{450} units) was 1.3-fold higher than that for patients with negative symptoms (0.14 ± 0.067 A_{450} units), but this difference was statistically

Number of patients (Sex)	**Abs to MBP, A_{450}/ml**	**Relative % of hydrolysis**	**$k_{cat} \times 10^3$, min^{-1}**
	Positive symptoms of SCZ		
	Parameters 1	**Parameters 2**	
1 (M)	0.32*	10.5**	9.8***
2 (M)	0.24	50.0	46.8
3 (M)	0.13	20.5	19.2
4 (M)	0.07	0.5	0.5
5 (F)	0.13	1.0	1.0
6 (F)	0.18	18.5	17.3
7 (F)	0.15	15.0	14.0
8 (F)	0.09	0.5	0.5
9 (F)	0.17	17.5	16.4
10 (F)	0.20	4.5	4.2
11 (F)	0.18	15.0	14.0
12 (M)	0.14	0	0
13 (F)	0.20	0	0
14 (M)	0.26	0	0
Average value	0.18 ± 0.066	11.0 ± 13.7	10.3 ± 12.9
	Negative symptoms of SCZ		
	Parameters 3	Parameters 4	
15 (M)	0.17*	50.0**	46.8***

Number of patients (Sex)	Abs to MBP, A_{450}/ml	Relative % of hydrolysis	$k_{cat} \times 10^3$, min^{-1}
	Positive symptoms of SCZ		
	Parameters 1	**Parameters 2**	
16 (M)	0.19	49.5	46.3
17 (F)	0.22	13.5	12.6
18 (M)	0.17	47.0	44.0
19 (M)	0.08	50.0	46.8
20 (F)	0.04	25.0	23.4
21 (F)	0.17	10.5	9.8
22 (M)	0.26	14.0	13.1
23 (F)	0.03	26.5	24.8
24 (M)	0.11	6.5	6.1
25 (F)	0.18	43.5	40.7
26(F)	0.16	43.5	40.7
27 (F)	0.08	0.0	0.0
28 (M)	0.12	0.0	0.0
Average value	0.14 ± 0.067	27.1 ± 19.6	25.4 ± 18.4
Correl. coefficient	Parameters 1 and 2 (0.28), Parameters 3 and 4 (0.10); Parameters 1 + 3 and 2 + 4 (0.04)		

*For each value, a mean of three measurements is reported; the error of the determination of values did not exceed 7–10%.

**Average values are reported as mean ± S.E; they were recalculated to standard conditions and complete hydrolysis of 0.33 mg/ml MBP after 5 h of incubation in the presence of 0.1 mg/ml IgG was taken for 100%.

***The average apparent k_{cat} values in the reaction of MBP hydrolysis were calculated using average RA values (% of the hydrolysis at fixed concentration of MBP**): k_{cat} = V (M/min)/ [IgGs] (M).

Table 2. Numbers of SCZ patients, their sex, and relative characteristics of patients antibodies.

insignificant ($P = 0.27$). Using the same approach and test system, it was previously shown that average index of anti-MBP antibodies for 25 MS patients is 0.8 ± 0.1 A_{450} units [79] and, for SLE patients, it is 0.38 ± 0.08 A_{450} units [75]. Thus, all SCZ patients analyzed by us demonstrated ~1.8-fold higher level of serum anti-MBP Abs than healthy individuals, but ~2.4-fold and 5.0-fold lower level than SLE and MS patients, respectively.

Electrophoretically and immunologically homogeneous polyclonal IgGs were separated from the sera of 28 SCZ patients and 15 healthy donors as described above. The homogeneity of the 150 kDa scz-IgG_{mix} and healthy-IgGmix (mixtures of equal amounts IgGs from the sera of 28 SCZ patients and 15 healthy volunteers, respectively) was confirmed by SDS-PAGE similar to [83] **Figure 1A**.

We have applied several of known rigid criteria described above. The most important of these criteria are given below: (1) electrophoretic homogeneity of scz-IgG_{mix} (**Figure 1A**); (2) complete

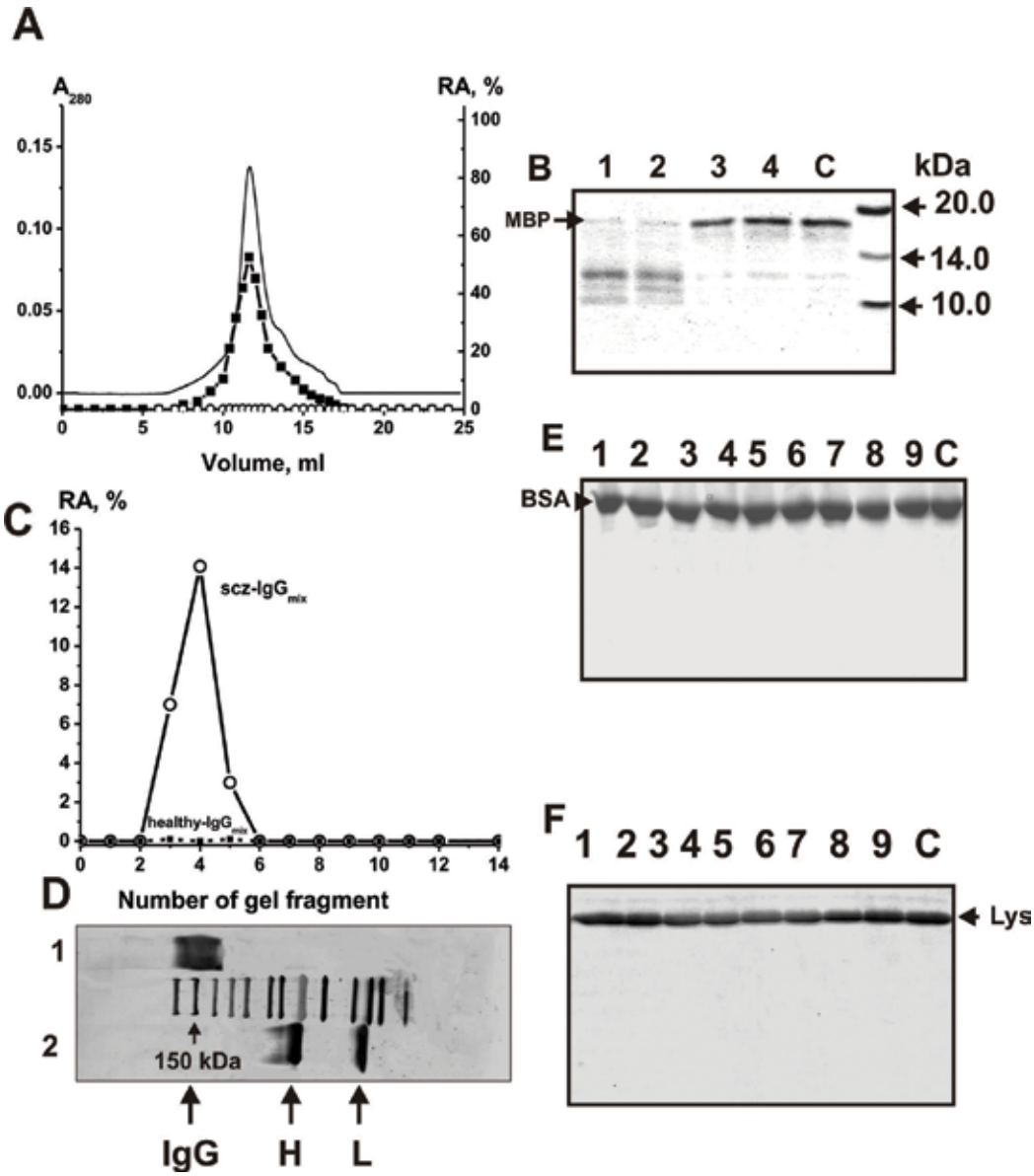

Figure 9. FPLC gel filtration of scz-IgG_{mix} on a Superdex 200 column in an acidic buffer (pH 2.6) after IgGs pre-incubation in the same buffer (A): (—), absorbance at 280 nm (A_{280}); (■), relative activity (RA, %) of IgGs in the hydrolysis MBP. A complete hydrolysis of MBP for 5 h was taken for 100%. Assay of MBP-hydrolyzing activity of purified scz-IgG_{mix} after SDS-PAGE in gradient 4-15 % gel, the gel was incubated under special conditions for renaturation of Abs (B). MBP (0.4 mg/ml) was incubated with 0.1 mg/ml scz-IgG_{mix} for 24 h (lane 1) or scz-IgG-1 (lane 2) and with healthy-IgG_{mix} (lane 3) or individual healthy-IgG-1 (lane 4), as well as in the absence of Abs (lane C). The RA (%) was revealed using the extracts of 2-3-mm many fragments of one longitudinal slice of the gel (C). The second control longitudinal slices of the same gels corresponding to IgG_{mix} before (lane 1) and after (lane 2) treatment with DTT were stained with Coomassie R250 (D). Analysis of possible hydrolysis of bovine serum albumin (BSA) (E) and hen egg lysozyme (Lys) (F) by scz-IgG_{mix} purified on MBP-Sepharose (lanes 1). Lanes 2-9 correspond to nine individual scz-IgGs, while lanes C to the proteins incubated in the absence of Abs (E and F).

adsorption of IgG_{mix} hydrolyzing MBP by anti-IgG Sepharose leading to a disappearance of the catalytic activity of the solution; (3) FPLC gel-filtration of scz-IgG_{mix} under conditions of "acidic shock" (pH 2.6) lead to revealing of the activity only in the peak corresponding exactly to 150 kDa IgGs (**Figure 9A**); (4) in contrast to scz-IgG_{mix}, healthy-IgG_{mix} did not hydrolyze MBP (**Figure 9B**); (5) Scz-IgG_{mix} purified on MBP-Sepharose hydrolyzed only MBP and was inactive in the hydrolysis of control proteins, bovine serum albumin (**Figure 9C**), and lactoferrin (**Figure 9D**); (6) scz-IgG_{mix} was separated by SDS-PAGE, and their MBP-hydrolyzing activity was estimated after the extraction of proteins from the separated gel slices (**Figure 9E** and **F**). The electrophoretic mobility of low molecular mass canonical proteases (24–25 kDa) cannot coincide with that of intact IgGs (150 kDa). Therefore, the detection of protease activity in the gel fragments corresponding only to intact IgGs together with the absence of any other proteins and activity bands (**Figure 9E** and **F**) provides direct evidence that SCZ IgGs possess MBP-hydrolyzing activity.

The RAs of SCZ IgGs in the cleavage MBP was estimated from the decrease in the intensity of Coomassie-stained MBP band after electrophoresis according to [76–81]. For quantitative estimation of the proteolytic activity, we have found a relatively low concentration of each IgG sample (0.05–0.3 mg/ml) corresponding to the reaction of the first order (1–24 h; 15–45% of conversion). This approach allowed us to normalize the relative activity, like in the case of determination of the specific activity of enzymes [102], to standard condition; relative % of MBP hydrolysis after incubation for 5 h in the presence of 0.1 mg/ml (0.66 μM) IgGs.

Among 28 individual SCZ patients, the RAs of IgGs at a fixed concentration of MBP (0.33 mg/ml) were absent for five patients (17.9%): 3 of 14 patients (21.4%) with positive symptoms and 2 of 14 patients (14.3%) with negative symptoms (**Table 1**). The average relative activity (RA, %) and apparent k_{cat} values (k_{cat} = V/[IgG]) at fixed concentration of MBP (0.33 mg/ml; 18.3 μM) were calculated (**Table 2**). The apparent k_{cat} values characterizing hydrolysis of MBP by 14 IgGs of patients with positive symptoms varied in the range 0–46.8 × 10^{-3} min^{-1} (average 10.3 ± 12.9) × 10^{-3} min^{-1}; M = 0.7 × 10^{-3}, IQR = (0.5–16.4) × 10^{-3}). The apparent k_{cat} values for 14 IgGs of patients with negative symptoms also varied in the range 0–46.8.0 × 10^{-3} min^{-1} (average (25.4 ± 18.4) × 10^{-3} min^{-1}; M = 24.1 × 10^{-3}, IQR = (9.8–44.0) × 10^{-3}). Overall, the average k_{cat} value of IgGs from patients with negative symptoms was approximately 2.5-fold higher than that for Abs of patients with positive symptoms (**Table 2**). The coefficient of correlation (CC) between the anti-MBP Abs titers (A_{450}) and RAs of 28 Abs was very low, 0.04. At the same time, CC for these values in the case of patients with positive symptoms (0.28) was 2.8-fold higher than that for patients with negative symptoms (0.10) (**Table 2**). According to Wald-Wolfowitz test, there is a statistically significant difference between k_{cat} value of IgGs from patients with negative and positive symptoms (P = 0.034). Interestingly, the CC (0.7–0.79) between the anti-MBP Abs titers (A_{450}) and RAs of Abs from SLE patients [8] was significantly higher than for SCZ patients.

It has been recently shown that abzymes against MBP from the sera of MS patients hydrolyze MBP at several clustered sites localized within four known antigenic determinants of human MBP and that four oligopeptides corresponding to these determinants of MBP are encephalytogenic and can play a negative role in the MS pathogenesis [79–82]. It is important that anti-MBP abzymes from the sera of SLE, MS, and SCZ patients hydrolyze MBP at the same four

sites of antigenic determinants and effectively cleavage all four 17–25-mer OPs corresponding to these four determinants [75–80]. It was shown, that anti-MBP abzymes of SCZ patients can also cleavage these four OPs: OP21 and OP25 were the best substrates of SCZ abzymes.

We have estimated the K_m and k_{cat} values for the hydrolysis of MBP, OP21 (YLASASTM-DHARHGFLPRRHR) and OP25 (AQGTLSKIFKLGGRDSRSGSPMARR) in the case of two individual preparations of SCZ patients. The initial rate data obtained at increasing MBP, OP21, and OP25 concentrations were consistent with the Michaelis-Menten kinetics. Different abzymes usually demonstrate a significantly higher affinity to substrates in comparison with canonical proteases [45–56]. The affinity of intact MBP for SCZ IgGs was (in terms of K_m values) in the range of 4.3–12.4 μM (**Table 2**), which corresponds to typical K_d (and K_m) values for Ab-antigen interactions. These K_m values for MBP of SCZ abzymes are to some extent comparable with the K_m for MBP (~0.6–2.7 μM) reported previously for IgGs from SLE [75–78] and MS (0.9–5.0 μM) [81] patients. Interestingly, the K_m values for scz-IgGs in the case OP21 and OP25 (49–770 μM) are to some extent lower compared with those for four OPs in the case of SLE. As it mentioned above, a detectable level of MBP-hydrolyzing abzymes was shown to be as an indicator of pre-disease, while increase in the activity of obvious pathology conditions of typical spontaneous or induced autoimmune diseases [63–68].

It was shown that DNase and RNase abzymes of autoimmune patients present a "cocktail" of Abs directly to DNA and RNA or their complexes with proteins and anti-idiotypic Abs against active centers of DNase I, DNase II, RNase and other enzymes hydrolyzing nucleic acids [92–96]. MBP-hydrolyzing Abs are produced from animals immunization with MBP and its encephalytogenic peptides [66–68]. In addition, immunization of experimental autoimmune encephalomyelitis (EAE) mice, a model of human MS, with myelin oligodendrocyte glycoprotein ($MOG_{35–55}$) leads to the production of both MBP- and DNA-hydrolyzing abzymes [66–68].

6. Abzymes with oxidation-reduction activities

Several publications show that some abzymes may form not only in patients with autoimmune pathologies but also in healthy humans. However, it is not currently clear which antigens can stimulate the formation of these abzymes in autoimmune patients and healthy donors.

Human organisms are constantly exposed to oxidative stress and various toxic components. The partially reduced oxygen species (O^{2-}, H_2O_2, and $OH^{\bullet}$) produced in all higher organisms and appeared in bodies through exposure to different compounds to ionizing radiation. They act as dangerous oxidants attacking lipids, proteins, DNA, and other different cellular components [103–107]. Oxidative damage of many cells has been considered as a very important pathophysiological factor in the development of many different diseases such as carcinogenesis, aging, multiple sclerosis (MS), and SCZ. It is believed that MS and SCZ have different pathogenetic mechanisms. MS is a neurodegenerative chronic disease of AI nature, associated with structural damage to the nerve fibers myelin sheath, while SCZ has neurotransmitter nature. It was, however, demonstrated that the oxidative stress activation is a major factor in the MS and SCZ [108–114]. In the case of SCZ, the cellular metabolism changes associated with alteration in the activity of enzymes including antioxidant enzymes were revealed [109, 112].

Several enzymes protecting various organisms from oxidative stress are known. Mammalian, plant, and bacterial peroxidases, glutathione peroxidases, oxidoreductases, oxidases, and dismutases are mostly metal ions-dependent enzymes [107, 115–118]. Metal ions having the variable valence (more often: Fe_{2+}, Cu^{2+}, and Mn^{2+}) participate in a transfer of electrons in the reactions of oxidation-reduction, catalyzed by enzymes [118].

A comparison of catalase, superoxide dismutase, H_2O_2-dependent peroxidase, and H_2O_2-independent oxidoreductase activities of polyclonal IgGs obtained from the sera of healthy Wistar rats have been carried out [119]. Approximately, 83% of IgGs possess superoxide dismutase activity, but all IgGs oxidized 3,3′-diaminobenzidine in the presence (peroxidase activity) and the absence of hydrogen peroxide (oxidoreductase activity). Only 17% of rat IgGs were shown to possess catalase activity. It was shown that small fractions of IgGs and their $F(ab)_2$ and Fab fragments of IgGs from sera healthy humans oxidize 3,3′-diaminobenzidine in the presence of H_2O_2 through a peroxidase and in the absence of H_2O_2 through an oxidoreductase activity [120, 121].

It was shown that some electrophoretically homogeneous IgGs (and their F(ab) and $F(ab)_2$ fragments) from the sera of patients with SCZ (36.4%) and from healthy donors (33.3%) possess catalase activity [122]. As in the case of the abzymes described above, it was shown that the catalase activity of all IgGs is their intrinsic property (**Figure 10**). The catalase RA of IgGs from the sera of individual of SCZ patients on average was 15.8-fold higher than that of healthy volunteers. After extensive dialysis against EDTA chelating metal ions of IgGs, the catalase RA of IgGs, on average decreases approximately 2.5–3.7-fold; all IgGs possess metal-independent and dependent catalase activity.

External Me^{2+} ions added to non-dialyzed and dialyzed IgGs significantly increase their activity (**Figure 11**). $Co^{2+}$is the best activator of non-dialyzed and dialyzed IgGs, the activation of IgGs by Mn^{2+}, Cu^{2+}, and Ni^{2+} ions is substantially lower than by Co^{2+}. All IgGs demonstrate several individual different expressed pH optima in the pH range from 4.0 to 9.5. These data speak for the individual repertoire of catalase IgGs in every person and an extreme diversity of abzymes in their pH optima and activation by different metal ions.

In this connection, it should be marked that polyclonal IgGs against different antigens from the blood sera of patients with AI diseases and with different activities are usually very heterogeneous in their affinity for specific antigens and can be separated into many subfractions by chromatography on antigens-Sepharoses [75, 76, 79, 123]. Pools of polyclonal abzymes can contain different proportions of light chains of κ- and λ-types, Abs demonstrating different pH optima, having different net charges, metal-independent or activated by different metal ions, and characterized by different substrate affinities and specificities [17, 39–43, 124]. It was shown that small fractions of IgGs of all four subclasses (IgG1–IgG4) from autoimmune patients are catalytically active in the hydrolysis of different substrates [47–56]. For analysis of myelin basic protein- and DNA-hydrolyzing activities of monoclonal light chains (MLChs) corresponding to SLE phagemid library of kappa MLChs were used [125–129]. It was shown that some hundreds of different monoclonal light chains hydrolyze DNA and other ones cleavage myelin basic protein; all MLChs demonstrated very different physicochemical and enzymatic properties [125–129]. It should be assumed that the extraordinary diversity of these

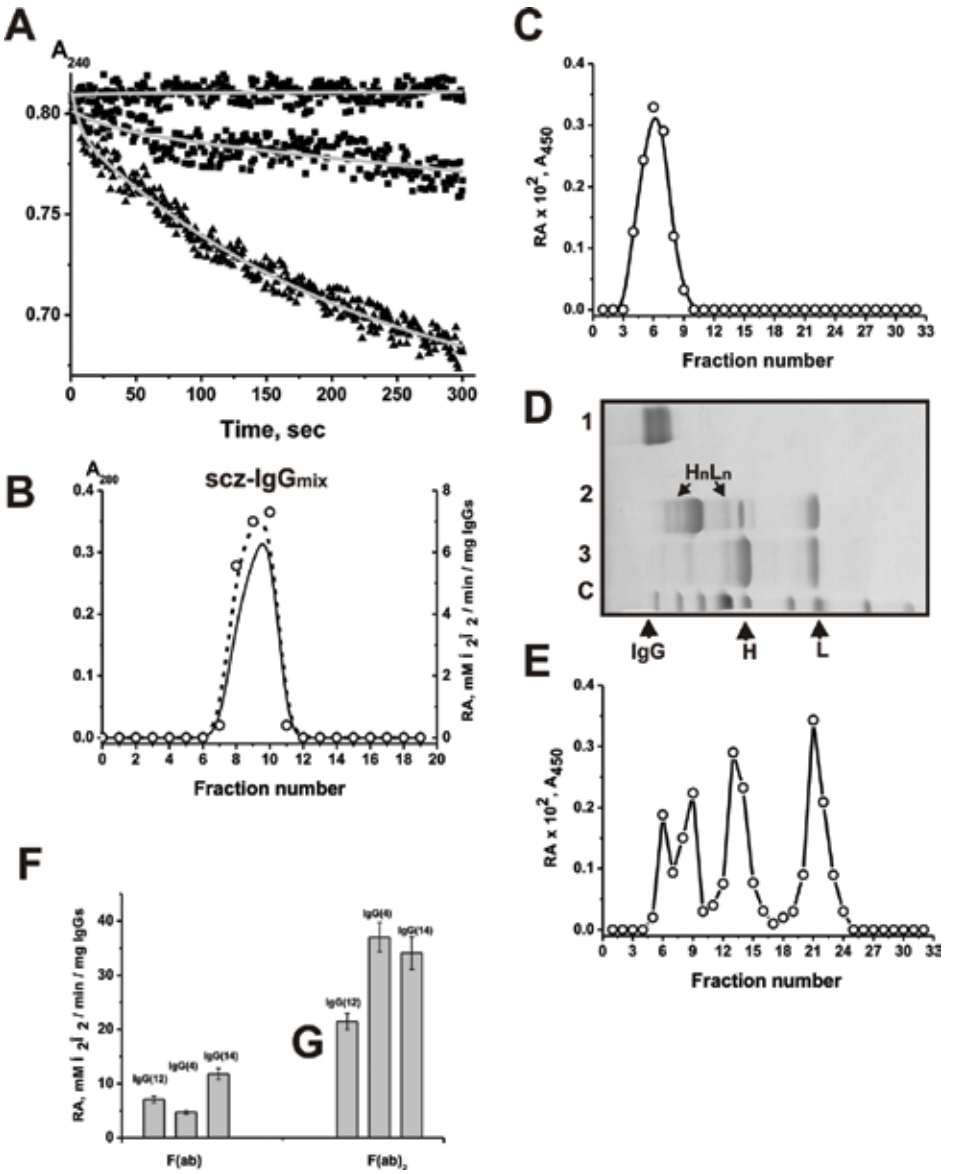

Figure 10. Typical time-dependencies of the decrease in 30 mM H_2O_2 absorbance at 240 nm (A_{240}) in the presence of 200 nM IgG-1 and IgG-11 as well as 2 nM IgG-8 corresponding to different individual patients (A). Checking of strict criteria proving that the catalase activity is intrinsic properties of scz-IgG_{mix}. Preparations of scz-IgG_{mix} (equimolar mixture of 22 samples) were separated by FPLC gel filtration on a Superdex 200 column in an acidic buffer Gly-HCl pH 2.6 after Abs pre-incubation using the same buffer (B): (o), relative activity (RA) of the IgG_{mix} in the degradation of H_2O_2; (—), absorbance at 280 nm (A_{280}); SDS-PAGE analysis of catalase activity of intact scz-IgG_{mix} (C) as well as separated H, L chains and their L_nH_n oligomers (E) in non-reducing SDS-PAGE using gradient 4–15%: Scz-IgGmix before (C) and after treatment of IgG_{mix} with DTT (E); lane 1 of panel D corresponds to panel C and lane 2 to panel E. The RAs (A_{240}/min) were revealed using the extracts of 2–3-mm fragments of one gel longitudinal slice of corresponding IgG_{mix} before (C) and after treatment with DTT (E). The control longitudinal slices of the same gels were stained with Coomassie R250 (D): lane 1 corresponds to intact IgG_{mix}, lane 2 to IgG_{mix} incubated with 40 mM DTT for 10 min at 30° C, lane 3 to IgG_{mix} boiled with DTT. Lane C (D) shows the positions of molecular mass standard markers. The relative activity of F(ab) and $F(ab)_2$ fragments of individual IgG-4, IgG-12, and IgG-14 (F). The average error of the initial rate determination from two experiments did not exceed 10–15%.

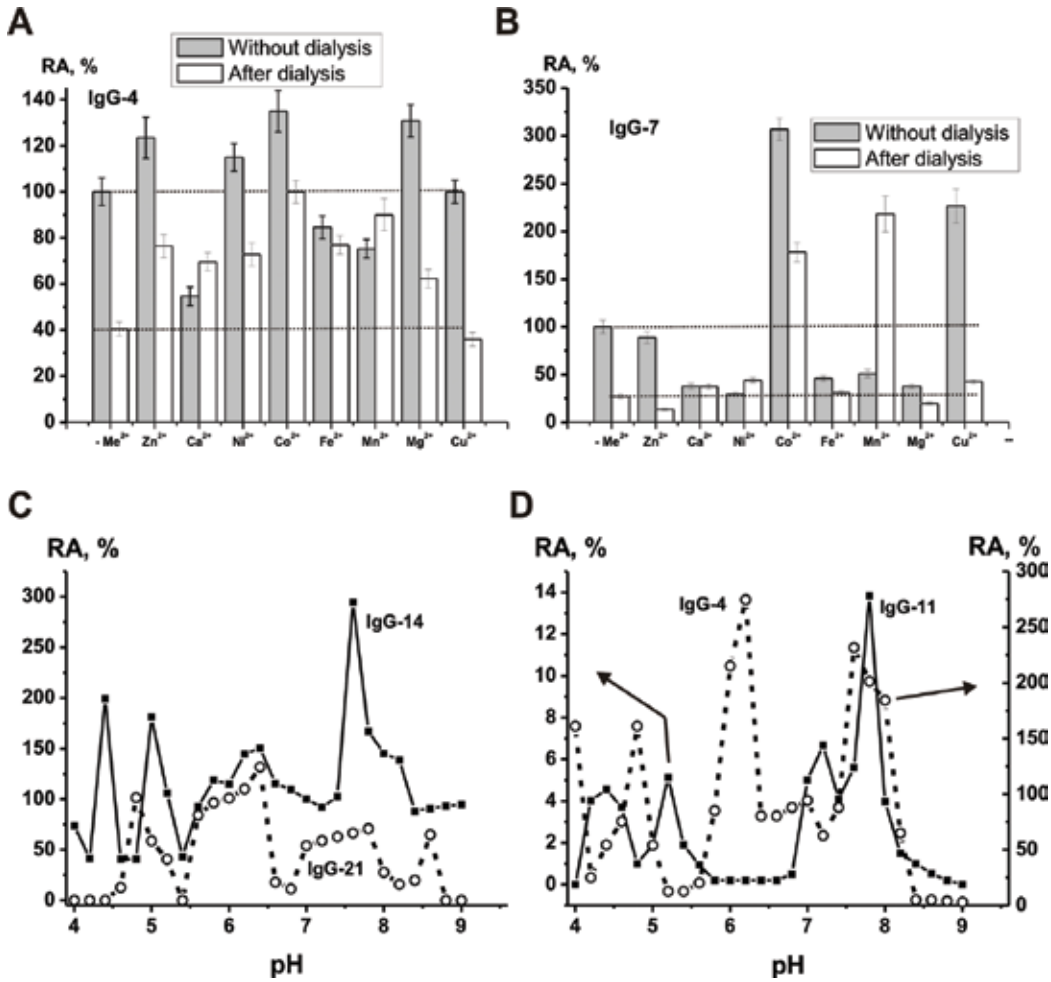

Figure 11. Effect of the dialysis of IgGs against EDTA for two individual scz-IgGs and different metal ions on the relative activity (RA, %) of dialyzed and non-dialyzed preparations (A and B). The RA of every non-dialyzed preparation was taken for 100%. Dependencies of the relative catalase activity of scz-IgGs on pH of the reaction mixture (C and D). All RAs of Abs before its preincubation were taken for 100%. The relative activity of IgG-14 at pH 7.0 was taken for 100%. All IgG preparations, metal ions, and conditions used marked on panels A–D. The errors in the determination of initial rate from three experiments in each case did not exceed 7–10%.

monoclonal light chains is mainly due to the significant differences in their variable regions responsible for substrate specificity and catalysis [125–129]. Heterogeneity is also observed in intact catalytic IgGs with kappa light chains, and it was shown that structural diversity (heterogeneity) might exist due to the constant region domain and specific role of metal ions of the catalytic light chains [130, 131]. A similar result of extreme catalytic heterogeneity is observed for abzymes with catalase activity.

It has been shown that immunoglobulins from humans and various animals have superoxide dismutase activity; they convert singlet oxygen $^1O^2$ into its reduced form $O^{2\bullet}$ [132, 133]. These abzymes use H_2O as an electron source and attach it to $^1O^{2*}$ to form H_2O_3 as the first intermediate of several consecutive stages leading to the formation of H_2O_2. These data are believed to

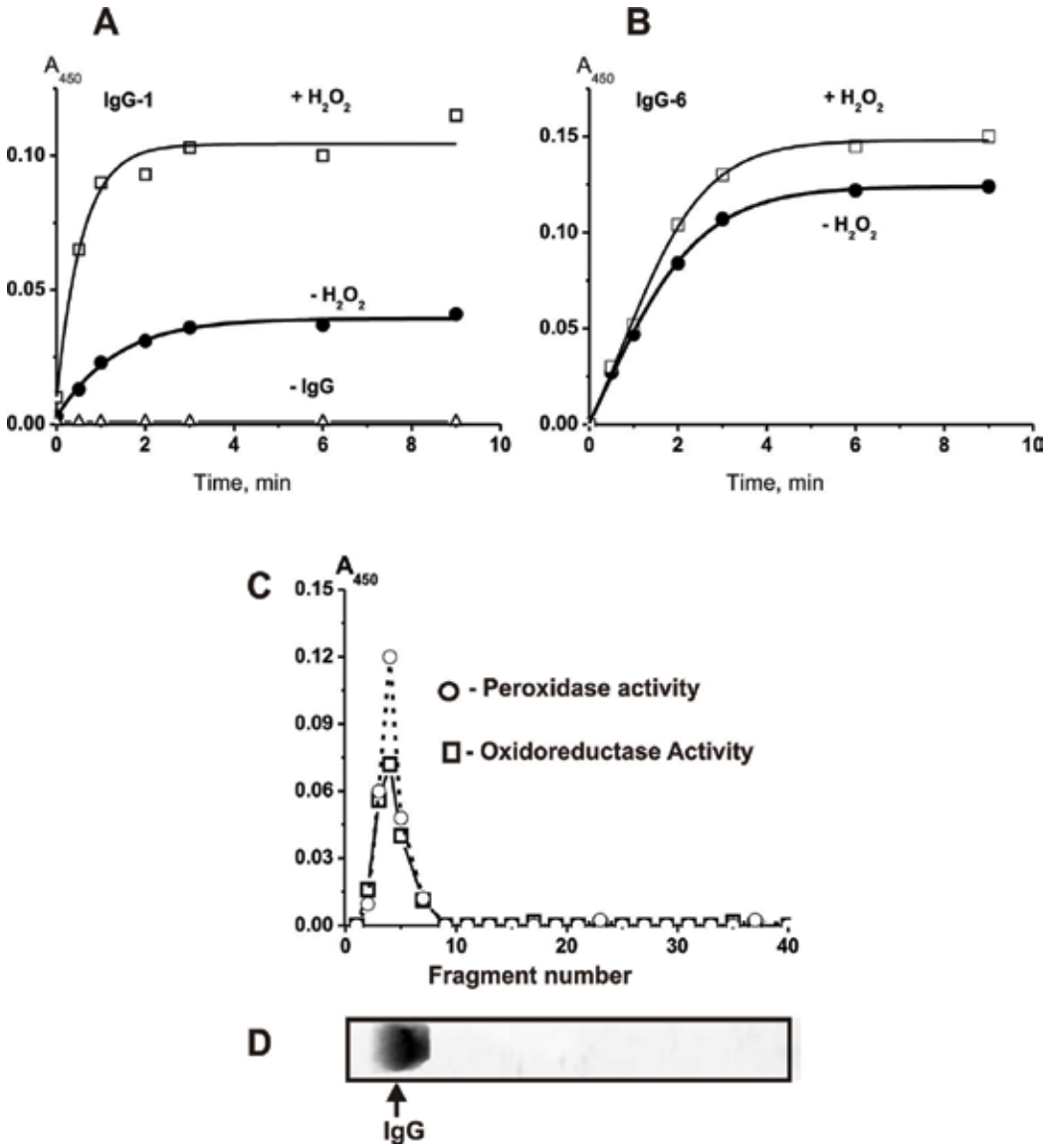

Figure 12. Typical kinetic curves of accumulation of a colored product (A_{450}) after DAB substrate oxidation by IgGs with peroxidase (in the presence of H_2O_2) (A) and with oxidoreductase (in the absence of H_2O_2) (B); activities in the oxidation of 3,3′-diaminobenzidine (0.2 mg/ml) in the case of 670 nM IgG-1 and IgG-6. Curve - IgG corresponds to the oxidation of the substrate in the absence of IgGs. SDS-PAGE analysis of peroxidase (o) and oxidoreductase (□) activities of IgG_{mix} (20 μg) (C and D). After electrophoresis, the 4–15% gradient gel was treated using special conditions for renaturation of IgG_{mix}. The RAs were evaluated using extracts of 40 gel fragments (2–3 mm); 20 μl of extracts were added to the standard mixtures and incubated for 24 h. The second band of the same gel was used to determine the position of intact IgG_{mix} (D); the gel was stained with Coomassie R250.

indicate the possibility of protecting mammalian organisms from $^1O^{2*}$ with Abs and raise the question of the possibility of a special evolution of immunoglobulins as a specific antioxidants of blood [132, 133]. For immunoglobulins, a mechanism has been discovered by which oxygen can be recovered and reused in phagocytosis, which indicates the possibility of the

involvement of the immune system in microbial regulation. Even more surprising is the discovery of abzymes of higher eukaryotes that catalyze the formation of ozone used by cells in phagocytosis [134]. Taking this into account, one can put that Abs with superoxide dismutase activity can catalyze the conversion of the superoxide radical into hydrogen peroxide, and the abzymes with catalase activity neutralize the harmful effect of H_2O_2.

It was shown that IgGs from the blood of healthy Wistar rats possess high H_2O_2-dependent peroxidase (hereinafter peroxidase) and H_2O_2-independent oxidoreductase (hereinafter oxidoreductase) activities in the oxidation of horseradish peroxidase substrate—3,3′-diaminobenzidine and some other aromatic amines, phenols, and quinones [135–138]. Interestingly, the same activities were detected in IgG from the blood of healthy people [120, 121]. The relative peroxidase activity of IgG of healthy people in the absence of external metal ions varies very much from donor to donor, but on average, it is about five times lower than in rat IgGs [120, 121].

Electrophoretically and immunologically homogeneous preparations of IgG antibodies were isolated from blood sera of 18 patients with SCZ and 14 healthy donors by affinity chromatography on Protein G-Sepharose followed by high-efficiency gel filtration as described above. Using rigid criteria, it was shown that the oxidation of substrates is an intrinsic property of these polyclonal antibodies (**Figure 12**). The comparison of H_2O_2-dependent peroxidase and H_2O_2-independent oxidoreductase activities of IgGs of SCZ patients and healthy donors in the oxidation of 3,3′-diaminobenzidine was carried. All IgG preparations of SCZ patients and healthy donors had these activities, but the apparent k_{cat} values varied in a very wide range (16.2–355.8 min^{-1}).

On average, the rate of oxidation of the substrate in the presence of H_2O_2 from the sera of SCZ patients and healthy donors was 1.3–1.5 times higher than in the absence of H_2O_2. The difference between the average peroxidase (1.8-fold) and oxidoreductase (1.5-fold) IgG activity from the sera of SCZ patients and healthy donors was statistically significant ($P = 0.008$). At the same time, the correlation coefficient of peroxidase and oxidoreductase activity of abzymes of SCZ patients was significantly higher (0.66) than for healthy donors (0.27).

The blood of healthy donors and patients with various autoimmune diseases including SLE and MS usually contains abzymes with amylase and ATPase activities [47–56]. In addition, the spontaneous and DNA-induced development of deep SLE-like pathology associated with a specific reorganization of the immune system in the case of autoimmune-prone MRL-lpr/lpr mice, leads to a production of IgGs hydrolyzing DNA, ATP, and polysaccharides [64, 65]. It was surprising that in the case of 18 patients with SCZ, amylase activity was detected only in IgG antibodies from one patient, but all 18 preparations were inactive in ATP hydrolysis. This indicates the possibility of the production of abzymes to various antigens in the case different autoimmune diseases.

7. Comparison of abzymes of patients with SCZ and other pathologies

It has been shown that antibodies hydrolyzing DNA, proteins, ATP, and polysaccharides can be considered the earliest and statistically significant markers of autoimmune pathologies in

human patients and experimental mice with autoimmune diseases [47–56, 64–69]. Abzymes are found already in the early stages of different diseases when there are no visible markers of specific AIDs, and changes in proteinuria, auto-antibodies titers correspond to typical ranges of these indicators for healthy individuals. The detection of abzymes is significantly more sensitive than the detectable ELISA markers since catalysis is characterized by the development of the reaction product due to a large number of enzyme turns and the possibility of increasing the catalyst turnover due to the increase in the reaction time. It makes possible to detect even small amounts of abzymes in preparations of polyclonal Abs with a relatively low but reliably tested activity.

Antibodies against DNA were detected in an increased concentration, compared with that in healthy donors, in only 17–18% of patients with MS and 37% of patients with SLE [57], while DNA-hydrolyzing Abs in 90–95% of patients with MS [74] and SLE [72, 73]. This is because the increase in auto-Abs titers in patients with AIDs occurs only in the late stages or with exacerbations of these diseases. Thus, reliable detection of abzymes, from our point of view, can be considered as an indicator of even a painful condition (the onset of pathology), and even more development of spontaneous or induced AIDS [47–56, 64–69].

To diagnose MS, a number of medical Poseur criteria are usually used [139, 140], but the final reliable diagnosis is made after the tomography showing "plaques" in the brain that appear in the late stages of the disease. The presence of anti-DNA Abs in patients with MS traditionally was considered only as one of the additional evidences of a system imbalance in immunoregulation, which has no independent pathogenetic significance. However, only anti-DNA Abs as the main component of the intracerebral IgG response was found directly in the brain plaques and the cerebrospinal fluid, and they bind to the surface of neuronal cells and oligodendrocytes [141]. These data were interpreted as evidence of the leading role of anti-DNA Abs in the pathogenesis of MS [141].

Despite the absence of signs that meet the criteria of Poseur, we assumed a preliminary diagnosis of the "initial stage of MS" in the case of three patients [69], since they demonstrated Abs with high DNase activity in their blood. Approximately 1.5 years later, the indicators of these patients began to meet the criteria of Poseur and after 2–3 years, the patients had "plaques" in the brain.

In this connection, it should be mentioned that the sera of healthy donors do not contain Abs with DNase, RNase, and MBP-hydrolyzing activities [47–56]. In addition, there were no detected abzymes with such activities in patients with weak autoimmune reactions. Currently, IgGs and/or IgAs and IgMs hydrolyzing DNA/RNA have been revealed in the sera of patients with SLE [72, 73, 142, 143], Hashimoto thyroiditis [144], diabetes mellitus [53], MS [74, 145, 146], tick-borne encephalitis [147], and HIV infection [148] demonstrating strong autoimmune reactions. As it was shown on the example of Hashimoto thyroiditis, the typical therapy of patients with thyroxine resulted only in a temporary change of the hormone concentration in the blood but did not affect the level of DNase abzymes. However, treatment of patients with an immunosuppressive drug Plaquenil leads to a significant decrease in DNase antibodies associated with an increase in concentrations of thyroid hormone, elevation of the thyroid gland functional activity, and improvement of the patient's clinical state [144].

It should be mentioned that the average concentration of Abs interacting with dsDNA for SCZ patients (0.25 ± 0.07 A_{450}/ml) is 2.5-fold higher than that for healthy donors (0.1 ± 0.02 A_{450}/ml), but lower than for MS (0.39 ± 0.26 A_{450}/ml) and SLE (0.66 ± 0.48 A_{450}/ml) patients [53–56]. At the same time, concentrations of anti-DNA antibodies in comparison with healthy donors are higher in 30% patients with SCZ, which is comparable with that for SLE patients (37%) [83]. In addition, 80% IgGs of SCZ patients possess detectable or high DNase activity. Moreover, all 100% of IgGs of SCZ patients have RNase activity, and they can hydrolyze not only different polynucleotides and cCMP, but also specific for this pathology microRNAs [83]. Thus, these data point to the development of autoimmune processes in patients with schizophrenia similar to those of classical AIDS: SLE and MS [83].

Interestingly, SCZ patients demonstrated ~1.8-fold higher level of serum anti-MBP Abs than healthy individuals, but ~2.4- and 5..50-fold lower than those for SLE and MS patients, respectively [75]. A feature people with MS and SLE is the development of abzymes hydrolyzing not only DNA, but also MBP and polysaccharides [75–82]. It was shown that IgGs from the sera and cerebrospinal fluid (CSF) of MS patients are active in the hydrolysis of MBP, DNA, and polysaccharides [149–151]. In contrast to healthy donors, Abs from the sera of 82% of patients with SCZ showed a reliably tested or high activity in the hydrolysis of MBP [100, 101]. As mentioned above, the researchers of the London medical Institute Oliver House advanced theory, according to which schizophrenia is the result of a lesion of immune system of the brain. The set forth above data reveals a number of similarities between SCZ and MS.

In this connection, it should be mentioned that development of SLE in autoimmune-prone MRL-lpr/lpr mice and changes in EAE-like (experimental autoimmune encephalomyelitis) parameters in C57BL/6 mice can occur spontaneously and may be accelerated by immunization of mice with DNA [63–65] or with MOG [66–68], respectively. It was shown that IgGs from the sera of control C57BL/6 mice are catalytically inactive. During spontaneous development of EAE, a specific reorganization of the immune system of mice occurred leading to a condition which was associated with the generation of catalytically active IgGs hydrolyzing MBP, MOG (myelin oligodendrocyte glycoprotein) and DNA. These processes are associated with increased proteinuria, changes in the differentiation of mice bone marrow hematopoietic stem cells and an increase in proliferation of lymphocytes in bone marrow, spleen, and thymus as well as a significant suppression of cell apoptosis in these organs. The strongest alterations were found after mice immunization with MOG. Thus, a significant increase in DNase and protease activities of abzymes were shown to be the earliest statistically significant marker of EAE development. In connection with these, it is important to note that abzymes hydrolyzing DNA, MBP, and oligosaccharides were found in cerebrospinal fluid of MS patients and their activity on average approximately from 30 to 60-fold higher than those from the sera of the same patients [149–151]. This may indicate that the development of autoimmune processes can begin already in the human brain.

In MS, SLE, and SCZ, anti-MBP abzymes can attack MBP of the myelin-proteolipid sheath of axons leading to a disturbance of conduction of nerve impulses [53–56]. Overall, the destruction of the myelin sheath and the production of MBP-hydrolyzing Abs can be a common phenomenon for some different diseases including SCZ. Interestingly, neuropsychiatric involvement to some extent similar to MS and SCZ patients occurs in approximately 50%

patients with SLE and carries a poor forecast [152]. SLE mostly affects the central neural system, and within its cerebral complications, it has a particular propensity—perhaps more than any other systemic inflammatory disease—to cause psychiatric disorders. Some similar neuropsychiatric indicators of disease common to SLE, MS, and SCZ were observed [152]. The production of abzymes hydrolyzing MBP as well as DNA and RNA even more powerful indicate the development of significant autoimmune reactions in patients with SCZ. Thus, in different patients with SCZ, SLE, and MS, there are, in some extent, similarities in the violation of the immune system, production of abzymes, and neuropsychiatric disorders.

As it indicated above, the sera of healthy donors contain abzymes with different oxidation-reduction activities. Therefore, at first glance, the detection of abzymes with such activities in patients with SCZ may not have a pathophysiological significance. However, in SCZ patients, a dysfunction of the glutamatergic system is shown [9–12], while misbalance of dopamine-glutamate homeostasis can result in the patient's development of generalized oxidative stress [13, 14]. In SCZ patients, the cellular metabolism changes are associated with alteration in the activity of enzymes, including antioxidant enzymes [109, 112].

The difference between the average peroxidase (1.8-fold) and oxidoreductase (1.5-fold) IgG activity in the oxidation of 3,3′-diaminobenzidine from the sera of SCZ patients and healthy donors was moderate but statistically significant ($P = 0.008$). At the same time, the average relative catalase activity of IgGs from the sera of SCZ patients was 15.8-fold higher than from healthy donors. These data on the oxidation-reduction enzymatic activities of antibodies seem to be important for understanding the possibility of protecting a person from oxidative stress with the help of blood immunoglobulins.

8. Conclusion

It was shown that similar to patients with typical autoimmune pathologies, SLE and MS, sera of SCZ patients contain IgGs hydrolyzing DNA, RNA, MBP, and abzymes with catalase, peroxidase, and oxidoreductase activities. As mentioned above, an appearance of abzymes with nuclease and protease activities, which are absent in the blood of healthy donors, may be used as the earliest markers of autoimmune reactions in patients with different autoimmune diseases. Therefore, one cannot exclude that abzymes with these activities may in addition to other different important factors cooperatively promote activation of neuropathologic and psychiatric mechanisms in SCZ pathogenesis.

SCZ patients show some similarity with MS and SLE patients in the development of the same medical, biochemical, and immunological indexes appearing especially in late stages of these diseases. Thus, it is obvious that early diagnostics of SCZ requires the use of all known independent methods to exclude SLE, MS, and probably other possible diseases leading to a formation of MBP-, DNA-, and RNA-hydrolyzing abzymes. However, even revealing of these abzymes on early stages of SCZ may be very useful for detecting of autoimmune reactions in such patients. It is known that SLE, MS, and SCZ patients are usually treated with different drugs. SCZ is known as the progressive mental illness with very different polymorphic symptoms, which are similar to typical autoimmune diseases associated in addition with

autoimmune reactions. Taking this into account, one cannot exclude that for a more effective treatment of schizophrenia, patients may be necessary to use some kind of medications suppressing the autoimmune reactions in this pathology. For example, it should be emphasized that the activity of MBP-hydrolyzing Abs attacking myelin-proteolipid shell of axons may be inhibited by MS therapeutic Copaxone [82].

DNase abzymes form SLE and MS patients are cytotoxic and induce apoptotic cell death. The decrease in activity of Abs with nuclease activities was achieved after treatment of patients with Hashimoto thyroiditis with Plaquenil [144]. It cannot be ruled out that any other drugs that are used to treat patients with other different autoimmune diseases can be effective in suppressing the autoimmune component in patients with schizophrenia.

In summary, as mentioned above, schizophrenia is not currently attributed to the typical autoimmune diseases. However, we have shown for the first time in several articles that polyclonal IgGs from the sera of schizophrenia patients possess DNase, RNase, MBP-hydrolyzing, catalase, peroxidase, and oxidoreductase catalytic activities, which are the earliest markers of autoimmune reactions. It means that immune system dysregulation including autoimmunity together with other factors can be important for the development of schizophrenia.

Acknowledgements

This research was made possible by grant from the Russian Science Foundation (No 16-15-10103) to G. A. Nevinsky).

Conflict of interest

The authors declare that they have no conflict of interest.

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Chapter 8

Epigenetic and Schizophrenia

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73242

Abstract

Schizophrenia is a complex psychiatric disorder characterised by the presence of positive, negative and cognitive symptoms that lack a unifying neuropathology. The absence of consistently replicated genetic effects, together with evidence for lasting changes in gene expression after environmental exposures, suggests a role of epigenetic mechanisms. In this chapter, we will focus on these mechanisms, such as DNA methylation, hydroxymethylation, histone modifications or non-coding RNA, as key mechanisms through which environmental factors interact with individual's genetic constitution which affect the risk of psychotic conditions throughout life. Due to the advances experienced in recent years, it is to be expected that in the next decades, an increasing amount of data will provide us with a more complete landscape of the contribution of epigenetics to the development of mental disorders such as schizophrenia.

Keywords: schizophrenia, epigenetic, DNA methylation, histone modifications, human brain

1. Introduction

Schizophrenia is a complex illness characterised by different types of positive, negative and cognitive symptoms that affect all aspects of mental activity. This disorder has a world prevalence of 1%, but it is higher in first-degree relatives as well as in monozygotic twins.

Although one of the main repository of scientific publications (the US National Library of Medicine, accessible from www.pubmed.com website) compiles, on average, more than 6000 original research papers per year, we only have fragmented knowledge about the aetiology, development and accurate diagnosis of schizophrenia.

What are the causes of schizophrenia? Does the genetic background of the individuals play a role in predisposition, onset and progression of this disorder? Or are the environment and its

different types of pressures (stress, nutrition, diseases, etc.) responsible for the development of this disorder? For decades, the nature versus nurture debate absorbed efforts from scientist either from biological sciences to psychiatry professionals. However, recent advances indicate that this debate could be finally overcome. In fact, nature and nurture interact in different ways, and we can imagine this situation as a cycle. In a dynamically changing environment, stimuli should enter the cell where this information is 'interpreted' and a plethora of biological mechanisms are able to produce a molecular response. Usually, this molecular response implies expression of genes that, in due course, will generate an organic response to confront the initial stimuli. And the cycle begins again (**Figure 1**), allowing to the cell to maintain its homeostasis.

Currently, we can see the intimacy of this interaction at a molecular level and we can understand how a single cell (whether an epithelial cell or a neuron) is able to adapt to an environment that is in a constant change, whether they be minimum changes (for example, a new cellular interaction) or significant changes (from a pH change to microbe attacks or environmental catastrophes).

Certainly, cells do not carry a gene for every possible response against environmental stimuli; we therefore need another 'way of reading' the genetic information or, even more, another layer of information. In fact, genetic information tends to be rigid: it is hard to change it, and when it happens (what we usually know as mutations) it biological meaning is comprised from cell death to cell survival, through a wide range of decisions that clash with the dynamics of environment changes. Although this rigidity is key to passing all this information from generation to generation, it does not seem to be useful when the cell needs a quick, dynamic response to its medium.

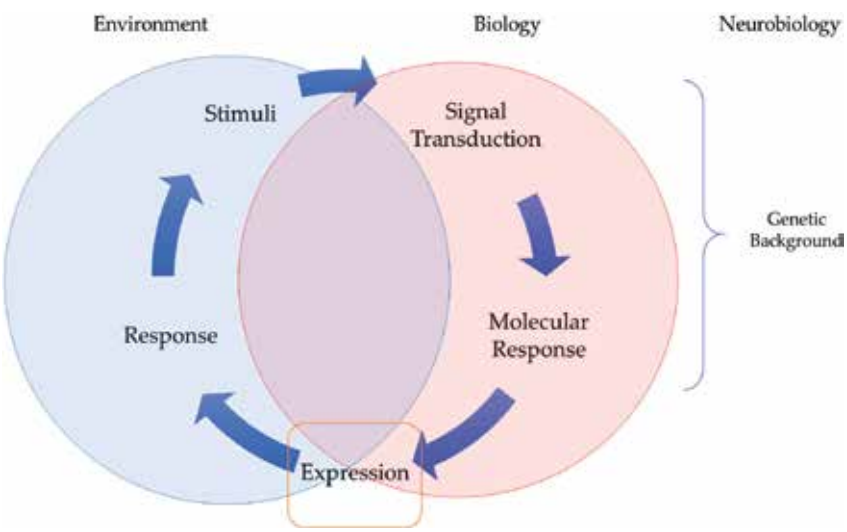

Figure 1. Interactions nature-nurture. Genetic and environment constantly interact to assure the maintaining of a constant internal medium for every cell, despite facing several types of stimuli.

In 1942, Conrad Waddington coined the term 'Epigenetic' to name the plasticity of genomes when facing environmental changes through his metaphor of marbles (representing cells in its developmental process) rolling down a hill, through valleys and forks (representing the environment) that affect the cellular fate (**Figure 2**) [1].

Since 1942, we have developed a more precise definition of epigenetic:

> *Epigenetic comprises all the molecular mechanisms that affect gene expression without changing the DNA sequence.*

As we will see throughout this chapter, epigenetics is both a new layer of information and a new way of reading the genetic information, leading to a gain in actual plasticity of the rigid genetic information.

In this sense, epigenetics could shed some light on elusive points of the aetiology, and general pathology of mental disorders, especially in schizophrenia, where interactions nature-nurture seems to be key to its onset [2].

1.1. Is epigenetic that important? A new layer of information

We can imagine epigenetic as a new layer of information that regulates the differential reading of genetic information, or the access to it. In turn, this regulation of reading or access to the genetic information is also regulated, as is common in living cells, by epigenetic mechanisms, too. Therefore, we can distinguish:

a. Mechanisms implied in differential reading of the genetic information: these mechanisms are responsible to selectively guiding the genetic expression according to minor (and sharply defined) atomic modifications of DNA. When these modifications are located in the right places along the DNA sequence, all the genetic expression can increase or decrease, thereby allowing the cells to response when facing dynamic changes. In this category, we could indicate the DNA methylation and hydroxymethylation.

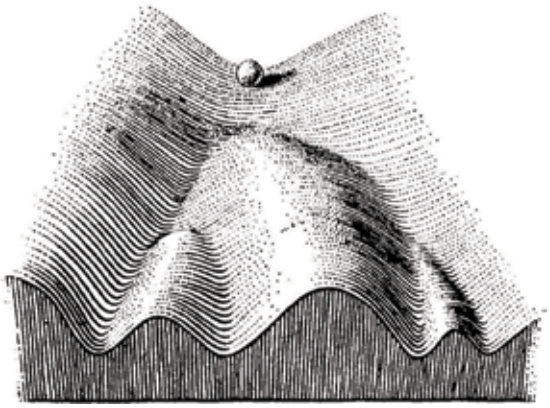

Figure 2. The epigenetic landscape by Conrad Waddington. With this metaphor, Waddington tries to illustrate how environment can influence the cells' fate during its developmental process.

b. Mechanisms implies in allowing (or avoiding) access to the genetic information: these subtle mechanisms encompass molecular changes that physically allow or avoid the access to DNA sequences or specific regions. In this category, we could indicate the post-translational histone modifications and the role of chromatin remodelling complexes.

c. Mechanisms that regulate epigenetic changes: the presence of feedback loops is common in living cells and epigenetic changes are also regulated in this way. There are several types of molecules (in particular, some types of RNA as we will see later in this chapter) that can regulate the epigenetic landscape in a healthy cell or be affected in an unhealthy cell.

The role of genetic background has been widely demonstrated in relation to the onset of schizophrenia. However, this factor is not unique as a causal one, and the individual needs to be in contact with several kinds of environmental factors to develop this mental disorder. In other words, the genetic information should interact with an environment to generate a schizophrenic phenotype, which may position epigenetic changes as key to understanding the molecular basis of this pathology.

As we can see, epigenetic changes could be subtle (such as specific atomic changes on a DNA base, or molecular changes in its associated proteins), or they can imply an actual remodelling of huge portions of chromatin, but always differently depending on the tissue, even more, depending on cell type. However, to understand how epigenetic mechanisms could trigger a mental disorder, we need to understand all the epigenetic changes as a whole, generating a framework instead of interpreting fragmented data. We call this framework the neuroepigenome. This new field implies efforts from several branches of Science in order to get a complete view of the epigenetic modifications of the nervous system which, in due course, will leads to a better understanding of pathological conditions.

Throughout the next sections, we will discuss the neuroepigenome from simpler modifications (such as DNA methylation) to the more extensive changes (such as the remodelling of chromatin), focusing on its role and recent advances regarding molecular pathology of schizophrenia. Given this field is still under frantic research, we will try to offer the most established (and replicated) facts, while leaving open doors to new developments and knowledge.

2. Differential reading of genetic information: DNA methylation and hydroxymethylation

The existence of DNA methylation was firstly proposed by Hotchkiss in 1948. More precisely, in those experiments, Hotchkiss was able to separate a modified cytosine by using chromatography. It was called 5-methylcytosine (5mc) and it was hypothesised that this form could be commonly present in nature. However, its role in regulation of genetic expression was not unveiled until the decade of the 1980s [3].

What is currently known as 'DNA methylation' is, in fact, cytosine methylation, and it consists of the transferring of a methyl group to 5′ carbon of cytosine, to generate 5mc. This modification is extremely active during embryo development, but it is relatively slower in

differentiated cells, and generates a characteristic pattern of methylation distributed along the genome. This pattern is not part of a random distribution but a tightly regulated distribution.

DNA methylation is frequently observed in cytosines adjacent to guanines, in the so-called CpG sites. This dinucleotide is mainly enriched at promoter sequences where it is repeated and grouped generating what is known as 'CpG island'. These 'islands' comprise around 1000 base pairs of the promoter region, with a high degree of conservation between species, becoming clear hotspots for methylation. Given the role of gene promoters, it was proposed that methylation acts as a regulator of genetic expression and this was the more replicated finding throughout research in life sciences. However, methylation was also observed in gene bodies, introns and intergenic sequences, with other functions that still remain elusive. On the other hand, it was also described methylation of non-CpG sites in murine cellular models or human stem cells, however its role is currently unclear, and it is under extensive research [4].

DNA methylation is a tightly regulated process and we can distinguish several types of enzymes that catalyse the necessary steps either to write or to erase this addition. The DNA methyltransferase (DNMT) catalysed the addition of methyl groups to cytosines. Three members of this DNMT family were described (DNMT1, DNMT3a and DNMT3b) and, despite its similarities, they have unique functions. DNMT1 catalyses the addition of methyl groups to the nascent DNA chain during replication, maintaining the methylation pattern of the cell lineage. However, DNMT3a and DNMT3b do not show specificity for hemimethylated sequences, so it was proposed that these enzymes are responsible for *de novo* methylation. However, how these enzymes target specific DNA regions or sequences are still unknown. There is also described a third isoform, called DNMT3L, that lacks its catalytic domain and it is mainly expressed during early development and in germinal cells. Although without its own catalytic function, this isoform could be associated to DNMT3a and DNMT3b to promote their methyltransferase activity.

On the other hand, the erasing of DNA methylation patterns could be a passive or active process. In mammals, DNA methylation in the form of 5mC can be actively reversed to unmodified cytosine (C) through TET dioxygenase-mediated oxidation of 5mC to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC), followed by replication-dependent dilution or thymine DNA glycosylase (TDG)-dependent base excision repair [5]. Instead, as a passive process, it was proposed that several chemical changes (deamination, oxidation) could generate a modified cytosine that activates the base excision repair (BER) system that eventually replaces that cytosine.

However, 5hmc it is also a modification that may have more biological function, different from an intermediary product of demethylation. In fact, high expression of this modification is found in brain tissue and during embryogenesis as well as in stem cells. It was proposed that this modification could influence the genome structuration during early phases of development. In fact, it was described that oxidation of 5mc to 5-hmc only takes place in paternal (but not in maternal) pronucleous [6, 7]. Regarding brain tissue, Wang et al. [8] reported a positive correlation between 5-hmc levels and cerebellum development in humans. Given that the previous methods to interrogate 5mc were unable to distinguish from 5hmc, this modification has only recently been assessed as an actual epigenetic marker. Therefore, many of its biological functions are currently under research.

2.1. DNA methylation as a research tool: main findings in schizophrenia

The development of methylation-specific polymerase chain reaction (MSP) allowed us to interrogate specific DNA sequences to assess its methylation status. In this technique, DNA is treated with sodium bisulfite that deaminates unmethylated cytosines to generate thymine (uracil). This conversion does not occur when there is a methyl group at the 5′ position of cytosine, which remains as a cytosine. This change allows researchers to generate specific primers for PCR amplification, in order to discriminate methylated from unmethylated alleles. This technique was a useful tool to understand the pattern of methylation in different gene regions. However, it was mainly applied to research promoter sequences trying to find correlations with gene expressions. In general, it was accepted that high levels of promoter's methylation mean decreased expression, whereas lower levels mean increased genetic expression. Of course, this is just a general rule and it is not applied to all genes. However, with this general idea, brain tissue of schizophrenic patients was evaluated. Although interesting, the main results are controversial. The base of this controversy relies on the usage of MSP, that only allows to interrogate some selected CpG sites, which leads to a fragmented information if we want to extrapolate (and correlate) to genetic expression. Keeping this situation in mind will facilitate us to understand some controversial findings in the next paragraphs.

Initial reports try to shed some light on the molecular mechanism of schizophrenia by using MSP and focused on the methylation changes of single genes. In this sense, in schizophrenic brain tissue, a higher level of methylation of GABA promoter regions that leads to lower levels of GABA mRNA was observed [9]. A similar finding was observed regarding *RELN* gene, that codifies reelin, a secreted protein involved in neurodevelopment with putative roles in schizophrenia onset [10].

Several other genes also showed changes of methylation pattern in schizophrenia, as those related to glutamate and serotonin signalling. For instance, hypermethylation of glutamate transporter genes or serotonin receptor genes (leading to a lower protein expression) was observed in schizophrenic brain [11, 12], but not in other studies [13].

On the other hand, specific changes of gene methylation carried out in specific anatomical regions could represent a more concrete regulatory event. For instance, hypomethylation of *COMT* gene (that leads to higher levels of COMT mRNA) may contribute to dopamine degradation in frontal lobes of schizophrenic patients [14], although it is a result that has not been replicated in other studies [13].

Finally, in a recent study, Alelú-Paz et al. [15] compared the DNA methylation pattern across the human genome in several normal and schizophrenic brain areas that have previously been linked to neuropathological features of schizophrenia, such as dorsolateral prefrontal cortex (DLPFC), hippocampus and the anterior cingulate cortex (ACC), reported several genes associated with cognitive impairment characteristic of schizophrenia, such as *LIF*, *PRKCE* or *CNTNAP2*.

We may indicate several studies related to single-gene changes in brain samples. However, currently scientists are more interested in understanding the epigenetic changes as a whole and, in fact, the recent development of Epigenetic-Wide Association Studies (EWAS) allow researchers to interrogate several thousand methylated sequences in a single chip. Even more, this technique is not restricted to gene promoter but to all genome, including gene bodies,

introns and intergenic regions, leading to a more complete scenario of methylation changes. It is relatively easy to assess around 450,000 selected sequences in a single chip. And the number of interrogated regions is rapidly increasing. In fact, by using this technique with schizophrenic brain tissues, it was demonstrated that changes in methylation occur along several portions of genes of glutamate transporters as well as dopamine and serotonin receptors, among others. In blood cells, this technique was also applied to study discordant monozygotic twins, where researchers observed several differentially methylated regions (DMR) between twins, in genes related to cell death, survival and cell movement [16].

By using EWAS technique, researchers are able to find several candidates as predisposition marks or putative biomarkers but, despite its higher resolution, EWAS generates a huge amount of information and the limits of its usage in diagnosis, treatment or prognosis of schizophrenia remains still elusive. It is still a novel field of investigation and its findings will need several years to clearly reveal molecular aspects of schizophrenia. In this sense, EWAS confounding factors are still under research. For instance, antipsychotics (as clozapine or sulpiride), smoking, age and several other environmental factors may also affect methylation and be detected by applying this approach.

An additional problem for using this technique is sample selection. Unfortunately, several EWAS were (and still are) carried out in peripheral blood or even in saliva samples [17]. More than a decade ago, it was completely demonstrated that epigenetic patterns are cell specific, so findings from tissues other than brain are controversial in their correlation to schizophrenia [17]. Even more, different anatomical zones (or cells) of brain may contain its specific epigenetic signature, leading to complications in the interpretation of results [15, 18]. Also, statistical analysis is key to ensure validity of results, therefore scientist need to be aware of these points to trust the technique and its results.

3. Accessing to the genetic information: histone modifications

If we were able to extend all the DNA molecule that lies in the nucleus, we would have a line measuring 2 m. In addition, all this information should be packed into a space measuring around 5 μm (1 μm is the millionth part of the meter). DNA condensation is key to ensure that all the genetic information is protected while is not in use, but it also need to assure that the required information could be accessible according to cells' needs. This condensation is achieved via several highly regulated steps, which begin with the formation of a DNA:protein complex. In doing this, a group of proteins called 'histones' are the key. Five histones have been described: H1, H2a, H2b, H3 and H4. Two molecules of every histone (except H1) are grouped to form a kind of flattened disk around which DNA is spun (approximately) two turns: this complex of protein and DNA is known as 'nucleosome' and it is the minimal structure implicated in DNA condensation. Histone H1 is located 'under' every nucleosome to keep them in place, and around 50 base pairs ahead another nucleosome is formed [19]. This sequence is repeated along the DNA molecule. In successive steps, groups of nucleosomes are gathered to form a highly condensed molecule. Finally, the mitotic chromosome represents the higher level of condensation of a DNA molecule.

This condensation is necessary to pack the DNA in the limited space of nuclei, but also to 'hide' genetic information, that may not be potentially necessary for the homeostasis of cells. Being more precise, it is well-known that a part of genetic information should not be physically accessible (for instance, the condensation of one chromosome X in males): this part of the genome constitutes what is called heterochromatin.

However, another part of genetic information should be accessible according to cell's needs which constitute what is called euchromatin. Although accessible, euchromatin information is still packed, so how this information is reached in a condensed molecule? As we previously indicate, eight molecules of histones form the protein core of nucleosome. As with every protein, histones have an N-terminal portion that is called the 'histones' tails' and are subject of different kinds of modifications: the post-translational modifications of histones. When a post-translational modification occurs, it implies a structural modification that is communicated as a nucleosome's opening or closing. Under these circumstances, genetic information is more accessible (or not) to transcription factors, which eventually promotes the gene expression.

Among these modifications we can find methylation, acetylation, phosphorylation, ubiquitination and others. These modifications can occur on many different residues, some of them harbouring more than one type of modification (i.e., residues can be either acetylated or methylated). Likewise, we can find different types of modifications on different amino acid residues. To complicate this picture, each modification carries implicit information that may indicate an opening (or closing) of nucleosomes, affecting the access of transcription factors to genetic information. Even more, modifications are different (and independent) in every tail of every histone. In the next paragraphs, we will describe some of the better-established histone modifications and indicate the most replicated role in regulation of gene expression. However, we need to take into account that the 'final conclusion' of all these modifications is, in fact, a balance between 'opening' and 'closing' signals, that eventually will lead to allow (or not) transcription factors to generate a mRNA.

3.1. Histone acetylation

One of the best-studied histone modifications is acetylation. It consists in the transfer of an acetyl group from acetyl coenzyme A to a specific histone lysine. This action is modulated by two enzymes, histone acetyltransferases (HATs) and histone deacetylases (HDACs): increases in former activity promote acetylation and the corresponding increase in gene transcription and increases in HDAC activity, which involves removing the acetyl group from histones, results in a repression of gene expression.

3.2. Histone phosphorylation

Histone phosphorylation is restricted to tyrosine (Y), serine (S) and threonine (T) residues. It has been described eight characterised phosphorylation sites on histones H2A, H2B, H3 and H4, which have been linked to specific cognate kinases. Although we still do not know in depth the role of histone phosphorylation, probably is important in the interpretation of combinatorial post-translational modifications which together regulate various biological processes, including gene transcription and DNA repair.

3.3. Histone methylation

Acting S-adenosyl-l-methionine as the methyl donor, the methylation of histones is carried out, mainly, by lysine methyltransferases (KMTs) and, to a lesser extent, by protein arginine (R) methyltransferases (PRMTs). More than 50 different histone methyltransferases have been described in humans, including SET1, MLL, SMYD3, ESET, G9a, SETDB or EZH2, that catalyse methylation of H3 at K4, K9 and K27 in mammalian cells.

On the contrary, histone demethylation, that is, the removal of methyl groups via histone lysine demethylases (KDMs) is, at the very least, a controversial topic. The discovery of KDMs suggests that this mechanism is not a permanent modification. To date, two classes of enzymes have been described: the amine oxidase-type lysine-specific demethylases 1 and 2 (KDM1A and KDM1B) and the Jumonji C (JmjC) domain-containing histone demethylases.

3.4. Histone ubiquitination

Clearly, the less well studied post-translational modifications. We know this mechanism acts by the addition of ubiquitin molecule to specific lysine residues on histone tails, which requires the sequential activities of ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2) and ubiquitin ligase enzymes (E3). It is important to note that histones are the most abundantly monoubiquitinated conjugates in the nucleus of mammalian cells, including ubiquitination at K119 on histone H2A, K34 and K120 on histone H2B, all of them associated with the transcriptional control of gene expression and the DNA damage response, including transcriptional reprogramming and DNA repair.

A summary of the aforementioned modification is shown in **Figure 3**.

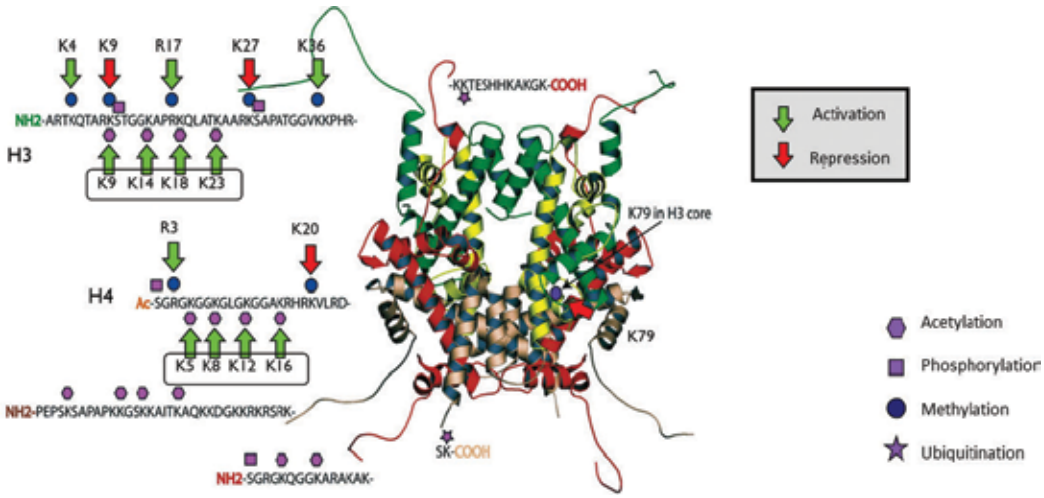

Figure 3. Main histone modifications and their roles regarding gene expression. The complexity of this information may facilitate gene expression or repression according to environmental (and internal) signals. The final combination of every modification will generate the proper response.

3.5. Histone modifications and molecular pathology of schizophrenia

Given their complexity, histone modifications were mainly studied in pathologies with well-characterised cellular and animal models. Unfortunately, the role of histone modifications is not clear for the development of mental disorders, although we find some post-mortem brain tissue studies that can be established as an interesting starting point.

Huang and Akbarian reported shifts in the prefrontal cortex chromatin surrounding GAD1 promoter accompanied by a decrease in GAD1 mRNA [20], whilst the latter author suggested a correlation between methylation of histone H3 at arginine 17 and down-regulation of several metabolic genes in schizophrenia [21].

Chase et al. [22] employed fresh-frozen parietal cortex post-mortem tissue, found significant increased levels of H3K9me2 in parietal cortical samples from patients with schizophrenia when compared to healthy controls, suggesting that initial inactivation of gene promoter activity at various schizophrenia candidate genes can result in gradual entrenchment of the heterochromatin state as a result of disease chronicity and disuse.

Other authors, focused on the role of interneurons in the pathophysiology of the disorders, suggested that acetylation of H3K9K14 correlated with gene expression levels for several schizophrenia-related genes, including GAD1, considered to be among the most frequently replicated findings in schizophrenia post-mortem brain [23].

Kurita and colleagues found a relationship between long treatment with antipsychotics and down-regulation of GRM2, a metabotropic glutamate 2 receptor, through decreased histone acetylation at its promoter region in the human frontal cortex, which could represent a promising new target for schizophrenia treatment [24].

Finally, in a recent paper, Schroeder et al. [25] reported decreased HDAC2 transcript in the dorsolateral prefrontal cortex of schizophrenia patients which represents a set of targets with demonstrated therapeutic relevance.

It is easy to see that we still need to understand more in depth the dynamic changes of histones during the development of mental disorders. Maybe, the main obstacle is not having proper models either animal or cellular. In this sense, the rapid development of techniques that implies stem cells (and induced pluripotent stem cells) may represent an option in the next years.

4. Regulation of genetic information by RNA molecules

A few decades ago, the huge amount of apparently useless DNA sequences lead scientist to coin the term 'junk sequences'. Nowadays, we know that a clear majority of the genome is transcribed, but only 2% generates proteins. So, a third epigenetic mechanism includes several activities carried out by different types of RNA molecules that were called 'non-coding RNA' (ncRNA) to differentiate from coding RNA that generates proteins.

The ncRNAs are classified according to their length: short non-coding RNAs (sncRNA) (length < 30 nucleotides and <200 nucleotides in general) and long non-coding RNAs (lncRNA) (length > 200 nucleotides). Among sncRNA we can find the so-called short interfering RNA (siRNA), microRNAs (miRNA) and Piwi-interacting RNA (piRNA).

Short non-coding RNAs are widely known, as well as the processes carried out to generate them. For a more extensive review of these molecular aspects, see Ref. [26]. In general, their functions are related to protein silencing by interfering the mRNA processing. Long non-coding RNA, as the name indicates, do not generates proteins, although their processing may be closer (or similar) to the normal mRNA. Furthermore, the length could easily reach more than 2000 nucleotides, they could be distributed either at nucleus or cytoplasm and their origins belong to introns or to transposable elements. Recently, it was observed a new type of lncRNA, which has its origin at the intergenic regions. This molecule was called long intergenic non-coding RNA (lincRNA).

In general, both types of transcripts are generated as a response to face environmental changes or as intermediary in other cellular processes. Even more, DNA methylation or histone modifications are targets of (or responsible for) their actions. For instance, some sncRNA are transcribed according to the methylation pattern of the specific gene (either at promoters or bodies), generating a siRNA that silence a target protein. On the other hand, the X chromosome silencing is mainly mediated by a 17 kb lncRNA that acts as an intermediary of histone methylations that generates 'repressive' marks (H3K27me3).

Although interesting and powerful, these mechanisms are poorly understood with regard to mental disorders and there is a clear lack of information. Regarding schizophrenia, there are relatively few reports that describe a general landscape or putative functions of non-coding RNA in development, onset, prognosis or diagnosis of this mental disorder. This is partly because this area is currently under active research (but mainly in oncology where ncRNA roles are better established). This also leads to generate only fragmented data with regard to other diseases that are different from cancer. Given this picture, we can summary some findings:

- Some miRNA showed association with schizophrenia risk in Chinese populations [27] although some controversy during its replication was generated [28].
- miRNAs were proposed as biomarkers of schizophrenia by assessing them in blood samples [29].
- Furthermore, miRNA seem to be dysregulated even in progenitor cells from schizophrenic patients [30].
- By using microarrays, lncRNAs were assessed in blood cells of schizophrenic patients and researchers found that downregulation of two lncRNA (from 40,000 tested lncRNA) were associated to better treatment outcomes and symptoms when patients were evaluated by using the Positive and Negative Syndrome Scale (PANSS) [31].
- A recent report proposed to lncRNAs as key elements in the dynamic of neurostructure and, in consequence, may have putative roles in schizophrenia development [32].

As we previously indicate, this are only selected items, and we hope that we will soon get a more complete view of the role of RNA molecules in schizophrenia development.

5. Epigenetics in the development of treatments: feasibility and challenges

Throughout this chapter, we summarised the main epigenetic findings focused on schizophrenic patients. Do these findings open any door to treatment development? Certainly, it is hard to predict the actual utility of epigenetic findings in drugs or treatment development and we may need to observe what happens in another pathology, mainly cancer. Nervi et al. [33], provide us with a more concrete point of view of clinical trials of epigenetic treatments for solid tumours.

With regard to schizophrenia, HDACs inhibitors are promising drug targets. In this sense, it was observed that HDACs expression may be associated to schizophrenia-like phenotypes [34] and that also their mRNA could be differentially expressed (and reduced) in prefrontal cortex of schizophrenic patients [25]. Valproic acid is a well-characterised HDAC inhibitor and it may be used in combination with clozapine (a demethylating agent) in order to promote chromatin remodelling, and eventually, to correct genetic expression deficits [35]. On the other hand, the role of HDACs isoform-specific inhibitors is still under frantic research. For instance, it was proposed that HDAC2 inhibition may help to treat symptoms in schizophrenia [24, 36]. Finally, methylating and demethylating agents lack specificity and its usage is restricted to research in cell models.

Despite the aforementioned, we must keep in mind that the possibility of treatment development arises from an extensive knowledge of the related epigenetic mechanisms about the pathology. In other words, firstly, we need the knowledge of basic processes and then we can develop successful treatments. Unfortunately, this could take time, and, in schizophrenia, we are at the beginning of a new research era, and still lack information about the epigenetic mechanisms triggered along its onset and progression. Therefore, in the next decade we will see an increase in our knowledge. The success of this approach will rely on sample selection, statistical accuracy and generated hypotheses by responsible and committed scientist aimed to obtain reliable results instead adding 'noise' to research in mental disorders [37].

6. Conclusions

Epigenetic mechanisms add a new layer of information that improves the cell plasticity against environmental changes. These processes are key to maintaining cellular health while frequently also being disorganised during the development of illness. Although there is no change to DNA sequence, these mechanisms play several roles in reading or providing access to the genetic information. Given this feature, epigenetic mechanisms were proposed as new targets to understand how a genetic background interacts with an environment to develop

schizophrenia. The first results obtained were promising, showing changes in methylation pattern of specific genes. However, this was only a piece of information and scientists are currently working in the development and application of more powerful techniques, such as Epigenetic-wide association studies. On the other hand, there is still an almost unexplored field regarding of role of histone modifications in the development of mental disorders. Great efforts are being made to unravel their role, although there is still a clear lack of information. We could indicate the same regarding other mechanisms as chromatin remodelling, therefore it is to be expected that in the next decades, an increasing amount of data will provide us with a more complete landscape of the contribution of epigenetics to the development of mental disorders as schizophrenia.

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Edited by Federico Durbano

In this book, with the involvement not only of clinical psychiatrists but also of neurobiologists, specific issues of psychotic disorders (mainly schizophrenia and mood disorders) are reviewed. The focus of attention ranges from therapeutics to the new frontiers of epigenetics. A special focus is on the individual reactions to psychosis (ranging from psychological ones to treatments and neurobiological basis).

Because of the rapid development of neurosciences, which are showing common underling factors to different phenotypical expressions of mental illness, we are facing an enormous growth of biological data, which is not always easy to interpret. The risk is to forget that we are relating to other individuals, with their stories, and, most of all, with their environmental resources and interactions. The contributions to this book will range from individual experience (a personal history of illness) through some aspects of individual management of illness (insight), from correct use of available psychosocial resources to the environment-gene relationships (epigenetics).

Published in London, UK

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ISBN 978-1-83881-500-4
9 781838 815004