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Dialogues in Clinical Neuroscience is a quarterly publication that aims to serve as an interface between clinical neuropsychiatry and the neurosciences by providing state-of-the-art information and original insights into relevant clinical, biological, and therapeutic aspects. Each issue addresses a specific topic, and also publishes free contributions in the field of neuroscience as well as other non–topic-related material. All contributions are reviewed by members of the Editorial Board and submitted to expert consultants for peer review.

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Controversies in psychiatry

Florence Thibaut, MD, PhD — Editor in chief

Abstract
Neuroimaging and recent genetics discoveries have raised many questions regarding the current diagnostic criteria of psychiatric diseases and the current classifications used, which are still based on subjective clinical assessment. Despite high-quality research in brain neuroscience and evidence-based guidelines in many psychiatric diseases, some therapeutic issues are still a matter of debate. These controversial issues will be discussed in this 20th anniversary issue.

Keywords: biomarker; controversy; genetics; psychiatry; precision medicine

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For the last 20 years, the journal Dialogues in Clinical Neuroscience has devoted each issue to a specific topic using review articles that introduce, in a highly integrated manner, basic neuroscience to the dilemmas faced by clinicians in everyday practice. The journal celebrates its 20th year of publication with this special issue on controversies in psychiatry.

At the turn of the 19th century, the science of psychiatry really began to develop, and the way that society treated the mentally ill gradually changed. Outstanding clinical descriptions of mental diseases were published by German and French (neuro)psychiatrists such as Griesinger and Charcot. Medical doctors and scientists began to understand how the brain works, and thus started the slow progress of mental health treatment. However, the first major breakthrough in the development of effective psychiatric drugs came out in the 1950s by serendipity. Yet, the introduction of effective antipsychotics for schizophrenia and mania, and antidepressants for depressive disorders, revolutionized the care of mentally ill patients and their outcome; many patients were finally able to live outside of the mental hospitals. From these discoveries, substantial progress was made in the understanding of the biological basis of psychosis and depressive disorders. However, the lack of specificity of these medications revealed a certain degree of overlap among clinical classifications of these illnesses. Furthermore the discoveries in the neuroimaging and genetics fields added an additional degree of confusion. In fact, common genes were identified between schizophrenia, autism, bipolar disorders, and intellectual disability. A whole neurodevelopmental spectrum of disorders was thus able to be identified. Altogether, these observations raised many questions regarding the current diagnostic criteria of psychiatric diseases and the current classifications used which are still based on subjective clinical assessment.

In contrast to many somatic diseases which already have implemented biomarkers, in psychiatry, we continue to build on subjective clinical assessment of clinical symptoms and syndromes. We need to develop biomarkers that can be measured objectively and evaluated as indicators of normal or pathological processes with a high level of sensitivity and specificity (Hoehe and Morris-Rosendhal, in this issue p 169). These biomarkers should also be easy to use and consistent across studies. They could be used for both early and differential diagnosis, personalized prediction of treatment response, and/or side effects. In precision or personalized medicine, the focus is on identifying which approaches will be effective for which patients based on genetic, environmental, and lifestyle factors. Noninvasive neuroimaging is a key area for biomarker development because it connects behavioral outcomes with structural, functional, and molecular mechanisms (Falkai et al, in this issue, p 179). Pharmacogenomics combines pharmacology and genomics to develop effective, safe medications and doses that are tailored to variations in a person’s genetic background (Hoehe and Morris-Rosendhal, in this issue p 169). Furthermore, integrating genomics, epigenomics, transcriptomics, proteomics, and metabolomics combined with neuroimaging may contribute to the identification of the pathways contributing to mental disorders, enabling a precision medicine approach to the treatment of individual patients. However, despite high-quality research in brain neuroscience and evidence-based guidelines in many psychiatric diseases, nonconventional approaches remain in the present practice of psychiatry and will be discussed in this issue (Schulz and Hede, in this issue, p 207). Finally, therapeutic issues regarding the use of antidepressants in minor depression or the length of main-
tenance antipsychotic treatment in schizophrenia remain a matter of discussion (Naber and Bullinger, in this issue, p 223; Davidson, in this issue, p 215).

REFERENCES

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A crisis of confidence was triggered by the disappointment that diagnostic validity, an important goal, was not achieved with the publication of Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The Research Domain Criteria (RDoC) project, which provides a framework for neuroscientific research, was initially conceptualized as an alternative to DSM. However, RDoC and DSM are complementary rather than mutually exclusive. From a historical perspective, this article argues that the debate opposing psychology and brain in psychiatric classification is not new and has an air of déjà vu. We go back to the first classifications based on a scientific taxonomy in the late 18th century with Boissier de Sauvages, which were supposed to describe diseases as they really existed in nature. Emil Kraepelin successfully associated psychopathology and brain research, prefiguring the interaction between DSM and RDoC. DSM symptoms remain valuable because they are the only data that are immediately and directly observable. Computational science is a promising instrument to interconnect psychopathological and neuroscientific data in the future.

Keywords: Boissier de Sauvages; ICD-10; ICD-11; RDoC; classification; DSM-5; psychiatry; nosology; Kraepelin; Wernicke

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20th anniversary issue

*DSM-5* criteria for Major Depressive Disorder (MDD) or Posttraumatic Stress Disorder (PTSD), is likely to have contributed to the inconclusive results of many drug trials. In parallel to the heterogeneity within categories, a categorical classification is not ideally suited to conducting research on dimensional or trans-diagnostic traits that may be common to different clinical entities. The object of the debate is now whether our current diagnostic categories, as defined by *DSM-5*, and soon by the *International Classification of Diseases (ICD-11)*, are still useful, or should they be discarded? In that case, is there a meaningful alternative? Should we: (i) remain faithful to *DSM*, (ii) embrace RDoC totally, or (iii) try to reconcile both? Psychiatry’s history—both recent and remote—suggests that the last proposition is the only viable one. The debate about the basis of classifications—ie, whether classifications should be descriptive, or whether they should be based on an etiological theory—has resurfaced whenever psychiatric knowledge was at a critical juncture or made new leaps.

**Proximal roots of the current validity crisis**

We may summarize the recent events in psychiatry by stating that *DSM-III* introduced reliability, in the form of a common vocabulary, after the era of psychoanalysis and antipsychiatry (both of which did not view classification as primordial). Clinicians and scientists supposed that this newly restored reliability was the long-expected prerequisite that would pave the way for future research, ultimately leading to validity. The current crisis of confidence was triggered by the disappointment that diagnostic validity, an important goal, was not achieved with the publication of *DSM-5*, despite optimistic promises and high expectations. In order to enhance validity, many proposals were circulated during the preparatory phase of *DSM-5*. One such suggestion was to rely more on dimensions and less on categories. However, dimensions were ultimately rejected because they were perceived as too cumbersome for use in everyday clinical practice; as is well-known, the dimensional model of personality was finally relegated to Section III. Another idea was to select markers derived from the wealth of data contributed by the very productive research into genetics, brain imaging, neurocircuitry over the last two decades. The *Research Agenda for DSM-5*, published in 2002, contained a proposal by Charney et al for a possible multiaxial system capable of accommodating neuroscience parameters (*Axis I: Genotype* [eg, genes related to disease, resiliency, or therapeutic response] *Axis II: Neurobiological phenotype* [eg, neuroimaging, cognitive functions, emotional regulation] *Axis III: Behavioral genotype*; *Axis IV: Environmental modifiers or precipitants*; *Axis V: Therapeutic targets and response*). After the abandonment of dimensions and biological markers, the publication of *DSM-5* in 2013 certainly gave us a very valuable instrument. However, disappointment was felt because the final product did not correspond to the paradigm shift that had been promised, and disappointment unleashed criticism.

**What is a good classification?**

Classifications are primarily judged according to their reliability and validity. In addition, they should be useful and practical. *Validity* means that our diagnostic categories describe real entities and not flawed concepts. This is a difficult endeavor if we take into account that we still ignore the etiology of most psychiatric disorders. Robins and Guze proposed a five-phase method for achieving diagnostic validity including: (i) clinical description; (ii) laboratory studies; (iii) delimitation from other disorders; (iv) follow-up studies; and (v) family study. Step 3 is traditionally a cornerstone of classification; it postulates that a diagnostic category should be homogeneous, and that “patients with other illnesses are not included in the group to be studied.” A cognate concept is that a valid diagnostic category should have distinct boundaries and should be separated both from normality and from other diagnostic categories by a “zone of rarity.” For example, PTSD should be distinct from the normal response to adversity, and patients with PTSD should not usually have major depression or anxiety disorders. More refined procedures to guarantee validity have been proposed more recently. Kendler differentiated antecedent, concurrent, and predictive validators. Andreasen suggested validators contributed by findings from genetics, neurochemistry, neuroanatomy, neurophysiology, and cognitive neuroscience. Andreasen’s proposals look like a harbinger of RDoC’s units of analysis. Validity is not the sole requirement, and other qualities such as utility and complexity also must be taken into account. Utility designates the practicable information that is conveyed by the diagnosis in terms of treatment planning, outcome, and sometimes etiology. An ideal classification should also be able to...
cope with the complexity of psychiatric disorders, which refers to the multiple reciprocal interactions between the various etiological factors.

Finally, classifications have to cope with the necessity to accommodate a large spectrum of disorders, ranging from quasi-neurological diseases to ailments that are heavily influenced by psychosocial factors. At the extreme, because of reimbursement issues, classifications have to provide diagnoses for normal persons who consult psychotherapists to sort daily life problems. Interestingly, in his General Psychopathology (Allgemeine Psychopathology), published in 1913, exactly 100 years before DSM-5 and RDoC,\(^9\) Karl Jaspers proposed that some psychiatric disorders followed the traditional medical model, whereas other psychiatric disorders, such as abnormal reactions or neurotic syndromes, were not medical disorders but variations of normality, which he placed in a so-called “Group III.”

Finally, a classification should be meant for the whole international scientific community and not confined to a country. This does not go without saying. Indeed, a study\(^{10}\) showed that France was one of the few countries where more than 30% of clinicians felt the need for a national classification of mental disorders (along with Cuba, Russia, India, Japan, and the People’s Republic of China) whereas less than 5% of interviewed persons shared this need in other European countries (eg, Germany, Spain, or the United Kingdom). A revised version of the Latin American Guide for Psychiatric Diagnosis (GLADP-VR)\(^{11}\) was published in Spanish in 2012, and a revised French Classification of Mental Disorders\(^{12}\) in 2015.

**It is very simple: we do not know what the universe is**

The main obstacle to validity is the sad fact that we ignore the ultimate causation of most mental disorders. In 1952, the Argentine writer Jorge Luis Borges\(^{13}\) described a fictitious Chinese encyclopedia, entitled “Celestial Empire of Benevolent Knowledge” that classified animals as follows: (a) belonging to the emperor; (b) embalmed; (c) tame; (d) suckling pigs; (e) sirens; (f) fabulous; (g) stray dogs; (h) included in the present classification; (i) frenzied; (j) innumerable; (k) drawn with a very fine camelhair brush; (l) et cetera; (m) having just broken the water pitcher; (n) that from a long way off look like flies. These categories are not mutually exclusive. For instance, a Chinese emperor might own a tame suckling pig, and ask a scribe to trace his name with a delicate camelhair brush. Though tame, this piglet, still young and playful, might one day shatter the water pitcher when gamboling. Obviously, the suckling pig is included in this classification (h), which means that the young animal would finally qualify for categories a, c, d, h, k, and n. This is an image of the comorbidity that afflicts DSM-III, -IV and -5. Borges used the system devised by this apocryphal Chinese encyclopedist to illustrate the point that every classification in the universe is “arbitrary and full of conjectures.” Most importantly, he further stated that “the reason for this is very simple: we do not know what the universe is.” (“La razón es muy simple: no sabemos qué cosa es el universo”). It is true that we know little about the etiology of mental disorders, and to cut a long story short, that’s why we are stuck with our diagnostic categories. In spite of that, Borges’ definition would boast correct reliability (if we were to use it, most of us would classify various animals in the same way).

**There is nothing new under the sun**

An examination of the early history of psychiatry suggests that the controversy about nosology, ie, the debate about whether classifications should be based on observable symptoms or on putative etiologies, is considerably older than the rift between DSM and RDoC. J. de Leon described the current debate as a feeling of déjà vu after 100 years.\(^{14}\) We may therefore conjecture that this debate is long-lasting and inherent to our discipline.

At the juncture between the epochs known as the Scientific Revolution and the Enlightenment, the first modern medical classifications were based on the system of scientific taxonomy developed by Carl Linnaeus (1707–1778). Boissier de Sauvages (1706–1778) maintained correspondence with him. He used Latin to compile his “Methodical Nosology” (1763), a systematic classification of all known diseases (2400 individual diseases), “in accordance with the method of Thomas Sydenham and Linnaean taxonomy.”\(^{15}\) The foreword to the posthumous French edition (1771) explains that observable features that exist only in the given disease, and distinguish it from all others, designate each disease. It was assumed that diseases could be captured as they existed in nature, and that “zones of rarity” separated them from one another. In Boissier de Sauvages’ nosol-
ogy (Table I), mental illnesses (Vesaniae) made up the 8th class of diseases; they were divided into four orders (Hallucinations, Morositates, Deliria, Folies anomales). Each order comprised several illnesses that were further subdivided into various types. Table I shows that each group comprises illnesses that are postulated to be caused by a common mechanism; an exception is the 4th order that seems to be a residual category (a kind of “Not Otherwise Specified” box).

The Encyclopedia compiled by Diderot and d’Alembert, the most influential publication of the Enlightenment, had an entry about “nosology” that was written in 1765 by Jean Joseph Menuret de Chambaud (1739-1815), a physician interested in the fields of semiotics and mental illnesses. As an adept of “neo-Hippocratism,” he believed that a physician should follow the method of directly observing the facts and should not get misled by theories. Menuret writes in the Encyclopedia that illnesses can be classified only according to their symptoms, since the knowledge acquired from the etiologies is always uncertain because it is speculative. Therefore, Menuret states that nosology should be simply equated with symptomatology. In his words, this approach is similar to the method used by the natural-

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<th>Class VIII. VESANIAE (Insanities)</th>
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<td><strong>Order I. HALLUCINATIONS</strong></td>
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<td>Vertigo</td>
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<td>Sufusio</td>
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<td>Hypochondriasis</td>
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<td>Somnambulism</td>
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<td><strong>Order II. MOROSITATES</strong></td>
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<td>Pica</td>
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<td>Hydrophobia</td>
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<td><strong>Order III. DELIRIA (Delusions)</strong></td>
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<td><strong>Order IV. ANOMALAE VESANIAE (Anomalous Insanities)</strong></td>
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<td>Amnesia</td>
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Table I. Mental disorders in Boissier de Sauvages’ Methodical Nosology (1763).
ist who creates a solid and clear classification of plants on the basis on the visible shape of fruits, flowers and leaves, instead of basing his system on the intimate structure of plants as seen with a microscope.

This botanical taxonomy, which was supposed to describe real diseases as present in nature, was demolished by Philippe Pinel (1745–1826), who criticized Boissier de Sauvages for his arbitrary choices, for mistaking isolated symptoms for proper illnesses, and for unduly expanding the number of categories (the same criticism was also made of DSM). Pinel narrated that he decided to disregard theoretical classifications and to rely on his own observations. Interestingly, Emil Kraepelin broke with the past in a similar way, and decided, after reproducing published knowledge in the first editions of his textbook, that it was time to start constructing a new system based on his own data (“Krankheitsbilder”). Kraepelin was painfully aware that his diagnostic categories were only syndromes (“Symptomenkomplexe”) and that the state of science did not yet allow him to describe real diseases (“Krankheitsformen”). In the very first edition of his textbook (1883), then called Compendium, Emil Kraepelin wrote “These syndromes will only acquire a deeper scientific basis when we will be able to establish that each of them has an understandable relationship with abnormalities of the brain cortex.” („Eine tiefere pathologische Begründung werden diese Symptomenkomplexe erst dann gewinnen, wenn es gelingt, ihre gesetzmäßige Abhängigkeit von krankhaften Störungen der Hirnfunktionen im einzelnen nachzuweisen.“)

At a time when we are learning how to derive the best from both DSM-5 and RDoC, Kraepelin remains a guiding figure. He was confronted with a concurrent school of all-brain nosology, but he combined different currents within a non-dogmatic and flexible frame. In fact, before RDoC, there has been a previous endeavor to map mental illnesses on the brain. Theodor Meynert (1833-1892) in Vienna was the first major representative of that current. Under his influence, his brilliant young student, Carl Wernicke (1848-1905), pursued the idea of localizing various brain lesions and deducing their clinical consequences. Wernicke published his seminal article on aphasia in 1874 when he was just 26 years old. It took Meynert 10 more years (1884) to publish a book with the revealing title: “Psychiatry: clinical aspects of the illnesses of the forebrain.” Arthur Schnitzler and Sigmund Freud were residents in Meynert’s clinic but, as is known, they decided to follow a different path. As Kendler wondered, “What if Wernicke, the one genuine competitor with Kraepelin for prominence in German psychiatry at the turn of the 20th century, had not died from a bicycle accident at the age of 52 in 1905?”, Kraepelin held Wernicke in high esteem, and he recruited a few of his disciples (eg, Robert Gaupp in Munich, or Karl Ludwig Bonhoeffer as successor in Heidelberg). Kraepelin knew that his nosological system was temporary and was bound to incorporate new data and undergo transformation. Even though Kraepelin thought that brain pathology was not advanced enough in his times to sustain a valid nosological classification, he consistently tried to connect psychopathology and brain pathology. When that became possible, he attracted the best brain pathologists to his clinic (Alzheimer, Nissl, Spielmeyer, and Brodmann) and the successive editions of his textbook contained precise descriptions of brain research.

**The way forward is reconciliation**

Even though DSM and RDoC have been viewed as antagonistic, most clinicians would consider today that they are complementary and synergistic approaches. The title of this article is a controversial question—can psychopathology and neuroscience coexist in psychiatric classifications?—that, in our opinion, can be answered most positively.

Jablensky recently expressed the thoughtful opinion that the way forward will be found in the conceptual reconciliation of both approaches. Realistically, we cannot function without a DSM-like classification. Clinicians prefer diagnostic categories, even though they are aware that categories are not valid in the sense that they are not discrete, and that they are only concepts and not real entities. However, diagnostic categories possess “utility” by virtue of the practical information they convey about treatment strategy and because they can be used for effective communication and decisions. On the other hand, the RDoC project is fascinating. It has been dubbed a “promissory note” and, in all likelihood, the note will be honored in a sumptuous manner, even though the period of time is unknown. RDoC has attracted considerable interest as a research framework. A March 2017 search of the NIH Reporter engine returned over 300 hits for funded research grants with “RDoC” as a search term, almost all in the clinical/translational area.
Also, the growth of computational science, and the ability to handle and decipher voluminous amount of data, will probably facilitate the integration of DSM and RDoC. DSM symptoms remain valuable in research because they are the only elements that we can observe directly. Strategies for the formal integration of DSM categories and RDoC dimensions have been delineated, for instance in a paper whose last author is Joshua A. Gordon, the current director of the National Institute of Mental Health. This paper discusses mathematical models where pathophysiological mechanisms, hidden from direct observations, may be inferred from their observed outcomes (ie, DSM symptoms and diagnoses, that are treated as observations).

Another reason to keep DSM, while making the most out of RDoC, is to break the pattern of destructive “wipeouts” in psychiatry described by Edward Shorter, a renowned historian of psychiatry. In lectures on “The fragility of psychiatric knowledge,” Shorter reminds us that psychiatry is the only medical specialty that has endured two “total knowledge wipeouts.” In the 1920s, the triumph of psychoanalysis wiped out the previous century of research in biological psychiatry. Psychoanalysis was similarly displaced by the return of biological thinking in psychiatry in the 1970s. As a mature discipline, psychiatry should be able to admit change without breaking, keeping up with the pace of neuroscientific research without throwing overboard centuries of precious psychopathological knowledge.

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REFERENCES

Introduction

What could a Vietnam War veteran, a female sexual abuse victim, a young man who has experienced an automobile accident in which his sister died, a father who has suffered burns to a large portion of his face, a girl who witnessed the death of her mother during a flood, a teenager who has been a victim of cyber bullying, and a liver transplant patient possibly have in common? Most likely the diagnosis of posttraumatic stress disorder (PTSD). This reactive disorder to a traumatic event occurs in certain clinical contexts with a prevalence above 20%.

It has been estimated that 70% of the population experiences at least one traumatic event in their lifetime, from childhood to old age.

The Vietnam War and the 2001 terrorist attacks on the Twin Towers and Pentagon are examples of recent events that have probably generated a major emotional impact in many subjects who have PTSD symptoms or the full-blown presentation of PTSD. PTSD has been widely discussed in the mass media, allowing the general population to become familiar with this diagnosis. Also, PTSD is an important issue in public health due to the individual, and family, consequences in community and society, as well as the financial burden that it
implies, and the challenges that have to be faced by the
development of preventive strategies.3

But, what is PTSD and how is it conceptualized?
The war registries include well-known descriptions of
soldiers who had to leave the battlefield due to acute
psychological symptoms, which occasionally persisted
for a long time. There are tales from Deuteronomy, histori-
ans, and classic writers (Homer, Shakespeare, and
Goethe) with characters presenting symptoms that con-
stitute today’s PTSD.

Goethe was very keen to identify the emotional effect
produced by shell explosions as a traumatic event and
emphasized that those symptoms are not accompanied
by physical damage. This fine observation can be related
to different trials that took place after the recent wars in
Afghanistan and Iraq, where mild traumatic brain dam-
age was linked to the appearance of PTSD.4-6

For the clinician, analysis of the psychopathologi-
cal phenomena and their evolution, together with a
possible neurobiological correlation and the therapeu-
tic response, constitute central elements to facilitate
diagnostic constructs. PTSD has evolved from its first
clinical descriptions in soldiers to the development of
models focused on symptoms within a network analysis
perspective. The psychotraumatology field is an area of
increasing progress and presents great challenges for
clinicians as well as researchers.

PTSD is a clinical condition of great complexity,
fully valid in clinical populations as well as communities;
this has been the subject of many studies and continues
to be a source of many controversies. The goal of
this paper is to review certain arguments that help the
clinician to clarify if PTSD corresponds to a diagnostic
entity, or can be exclusively considered within psychia-
tric pathology; if it should be approached as a systemic
disease or is best included as an operational syndromic
diagnosis.

History, definitions,
and diagnostic criteria

Different names have existed for a group of symp-
toms that today are conceptualized as PTSD. Initially, the
symptomatology observed in soldiers was key to identi-
fying this new field of psychopathology. Toward the end
of the 19th century, the concept of traumatic neurosis
arose from the psychoanalytic current of thought, in
which stress was put on the psychic conflict as a trigger
of posttraumatic symptoms. This diagnosis was applied
to the civilian population: to railroad accident survivors
who presented psychological symptoms.

On the other hand, traumatic hysteria (from Janet
and Freud) could have dissociative and amnesiac phe-
nomena, that have become relevant as PTSD predic-
tors when they appear as the initial trauma response. In
this respect, World War I left as a legacy the incorpora-
tion of “shell shock” as a diagnosis, the importance of
etreatment of the acute post-trauma symptoms on
the battle front (today named psychological first aid),
and finally the concern for those soldiers who required
prolonged hospitalizations, who were discharged from
the army, and could receive economic compensations
for the psychiatric symptoms. The recognition of shell
shock as a diagnosis of disease was also controversial,
and its critics stated that it was only to justify the high
number of deserting soldiers.7

During the Vietnam War many soldiers were decom-
misioned for psychiatric reasons, being diagnosed with
Post-Vietnam Syndrome. This definition was adopted in
1970 and had huge repercussions in the psychiatric en-
vironment and the media.8

A 1972 trial with a group of United Nations Peace
Corps soldiers during the Congo civil war did not find
any differences in the prevalence of psychological man-
ifestations and/or mental disease among those exposed
and not exposed to combat.9 This result confirms that
the condition of volunteer soldiers could be a protec-
tive factor for the appearance of PTSD.

It is important to point out that the 1952 first edition
of the Diagnostic and Statistical Manual of Mental Dis-
orders (DSM) included the diagnosis of Gross Stress
Reaction, in which the core issue was the overwhelming
fear response to an extreme stressor in a subject with
normal personality. This diagnostic category did not ap-
pear in DSM-II. During the preparation of the DSM-III
the discussion to reinstate that diagnosis arose. Nancy
Andreasen led the study group and defined the new
PTSD construct in 1980.10 PTSD was conceptualized
based on three main groups of symptoms: re-experienc-
ing the traumatic event, avoidance behavior, and hyper-
vigilance phenomena.

In 2001, Summerfield criticized PTSD diagnosis and
stated that this corresponded with an invention that
was useful for sociopolitical and not medical reasons,
and argued that having a psychiatric diagnosis did not
necessarily imply having a disease.11
In DSM-5, PTSD migrated from the group of Anxiety Disorders to a new group named Trauma- and Stressor-Related Disorders. Among its diagnostic criteria are included 20 symptoms divided into four groups: intrusion symptoms, persistent avoidance of stimuli, negative alterations in cognition and mood, and alterations in hypervigilance and reactivity. A dissociative subtype is also recognized; this is under full study to develop better therapeutic alternatives, as it presents a severe progression in most cases.

In the upcoming 11th version of the International Classification of Disease (ICD-11), the diagnostic criteria for PTSD will include six symptoms that fall into three major categories: re-experience, avoidance of traumatic memories, and feelings of continued threat which are expressed by excessive hypervigilance or exaggerated alertness.

An important aspect to determine if the symptomatology in fact corresponds with PTSD is related to the number of criteria according to the diagnostic system being used. In that sense, a series of diagnostic models have arisen in an attempt to assess symptoms more accurately. Ideally the chosen model should neither be very complex, which would make its application difficult, nor so simple that it cannot identify those patients with symptoms that are characteristic of PTSD.

Recently the DSM-5 criteria were compared with those of the proposed ICD-11 in three groups of trauma victims and it was found that for university students with the three-factor ICD-11 model (re-experience, avoidance, and threat) the frequency of PTSD was lower than in the 7-factor hybrid model of DSM-5 of Armour et al that includes intrusion phenomena, avoidance behavior, negative cognitive as well as mood disorders, anhedonia, externalizing behaviors, anxious hypervigilance, and dysthymic hypervigilance. On the other hand, no differences were found for patients with chronic pain and military personnel using both diagnostic systems. Thus, the use of a diagnostic system will influence the precision that can be achieved in identifying those patients with PTSD.

The traumatic event

It is essential to establish what constitutes a traumatic event. Are the characteristics of the experienced event enough to categorize the event as traumatic, or is it from the subject’s reaction that a traumatic connotation can be given to a certain experience? Initially the traumatic event was associated with war situations and focused on soldiers’ experiences, such as life-threatening experiences, the deaths or serious injuries of their partners and comrades, or atrocities suffered in captivity or concentration camp experiences. Once the term PTSD was officially included, the stressor qualified as traumatic only when it exceeded the usual life experiences.

Death threats, rapes, child abuse, and natural catastrophes were included. Intentional and non-intentional events were clarified in terms of being caused by man or as a result of a natural catastrophe. The initial reaction of fear, horror, or helplessness had special relevance. Later on, the experiences considered to be traumatic were extended and included, for example: motor vehicle accidents, panic attacks, diagnosis of a certain illness, the experience lived by immigrants, psychological family violence, occupational accidents, and spontaneous and provoked abortions, assaults, etc. Since traumatic stressors are no longer extreme, the question arises as to whether it is the response with post-traumatic symptoms that allows the connotation of “traumatic” to be assigned to the event. For instance, the accidental amputation of the distal phalanx of the fifth finger in a cosmetic saleswoman can be a traumatic event. If the integrity of her body and good personal presentation are very important for her job, this accident and its physical consequences can facilitate the development of a PTSD and even progress to a chronic disease, ending in disability pension due to being unable to reinitiate her work activity.

In conclusion, the definition of the triggering event as traumatic is a controversial aspect. Is it a trigger per se, or because retrospectively the condition of traumatic is assigned to this stressor due to the posttraumatic phenomena of the one who suffers it? The central issue would be the way in which the subject processes the specific event (ie, guilt or anger) and the appearance of responses of re-experience, avoidance, and hypervigilance.

PTSD is a diagnostic term that very clearly reflects a model of mental disease. An identified psychological stressor is required to generate the classic symptomatic triad together with other psychopathological phenomena. There is also a neurobiological correlate of stress response to threat. In this case the psychological and biological elements of the mental disease intertwine very well. Today’s knowledge on PTSD does not allow the
etopathogenetic separation between an organic origin and a psychological motivation. Psychological trauma is accompanied by neurobiological manifestations, which are increasingly better identified, in animal models as well as in PTSD patients.21-27

**New constructs for PTSD**

ICD-11 is *ad portas* of being launched and, according to factorial models, two diagnostic entities with different symptom profiles have been defined: PTSD and complex PTSD. The first one is characterized by three main symptoms (re-experiencing the event in the present, deliberate avoidance of traumatic memories, and a sense of current threat), which at the same time include two symptoms of each factor. Symptoms profiled in PTSD are based on fear and anxiety caused by trigger stimuli related with trauma. In complex PTSD, there are other psychological symptoms that arise early, repeatedly, and prolonged in time, and have been named Disturbances in Self-Organization, which affect emotional regulation, interpersonal relationships, and identity.

When comparing diagnostic criteria of ICD-11, using the International Trauma Questionnaire, with those of the DSM-5 for PTSD (the PTSD checklist for DSM-5 or PCL-5) in trauma victims it was found that a higher percentage of cases could be detected with this last system.28 Equivalent results were found in a group of Ukrainian adults who were displaced.29 The choice of one diagnostic system or another can have an impact further from the purely medical, in the assignment of handicap pensions or insurance coverage.

**PTSD, symptomics, and network models**

During the 19th and a large part of the 20th century, psychiatry privileged symptom analysis and progression to define the diagnostic constructs. Neuroscience development in recent years has been progressively incorporating this new knowledge into the etiopathogenesis of mental illnesses; nevertheless we still do not rely on diagnostic systems in which the biological elements have greater importance. Beyond the classical categorical diagnostic approach, the network-based model allows greater comprehension and a better approach to the psychopathological complexity and individual characteristics.30

A research field called Symptomics Research has risen in recent years, which focuses on symptom analysis and its three cornerstones: i) the manner in which a relationship between a certain symptom and biological markers is established, risk factors, therapeutic response, and functional deterioration; ii) potentially causal relations among symptoms based in symptom networks; and iii) a more precise psychopathology at the level of individuals instead of heterogeneous groups of patients.

There is some progress in the trials that research PTSD symptoms, by means of network structures, in different populations of patients (refugees, terrorist attack victims, adults with prior history of institutional abuse during their infancy, and adult victims of childhood sexual abuse).31-34 While the methodological issues of these trials are complex, some promising results have been obtained in relation to the connections among different factors that integrate the network among symptoms, identifying those that are key. For example, in a group of severely traumatized refugees, the central symptom found was emotional cue reactivity and the intrusive phenomena were related to difficulty in remaining asleep. This clinical profile allows a better treatment approach.31

Within this approach it would be desirable to include temporal and dynamic data that facilitate the modeling of a temporal dynamic of the causal systems through time, and thus offer better prevention strategies or more specific interventions according to a more personalized perspective in medicine. It is also important to have more specific relationships available between symptoms and neurobiological variables. This new approach to psychopathology offers a change in paradigm from a static view as it occurs with the DSM or ICD systems, in which the symptoms are seen as passive consequences of the underlying disorders, to a dynamic one of causal influences and vicious circles as proposed by Armour et al.35

**The contributions of Research Domain Criteria**

Since 2009, National Institute of Mental Health has been developing a classification system that includes diagnostic elements contributed by neuroscience, cognitive sciences and other areas that contribute information for a new nosology that facilitates more
personalized medicine for mental disorders. The Research Domain Criteria (RDoC) project, conceived as a research tool and not for clinical application, is based on the fact that mental disorders affect the brain and compromise specific areas and circuits that participate in behavior, cognition, and affectivity. As a result, the diagnosis must be wider than the DSM categories and also include symptoms as well as biological features.

The five domains into which the RDoC matrix is divided are the systems with negative value, systems of positive valence, cognitive systems, social processes, and alert/regulatory systems.

On the basis of this, we can understand that DSM categories cannot be considered as references, but, starting from information that is gathered, new diagnostic groups should arise based on symptoms with a neurobiological correlate, which could facilitate new therapeutic and preventive strategies. RDoC criteria for PTSD have been designed for adults as well as for children. After reviewing the criteria for PTSD research, Schmidt and Vermetten have proposed incorporating emotional and stress regulation constructs, and consciousness status, which will allow the better identification of some subtypes of PTSD.

The theoretical model of the hyperarousal subtype of PTSD is a good example to understand the complementation of the symptoms with the neurobiological basis that support them according to RDoC criteria.

The psychological trauma

Psychological trauma and one of its consequences, PTSD, include central elements of the human being. Vulnerability to having a maladaptive response in the face of a threat and resilience to adequately cope with a traumatic event are conditions that pertain to each subject with biological and psychosocial factors in its construction. Clinical exploration of a traumatic situation or the suspicion of its presence is difficult for the health professional as well as for the subject who has experienced it; and thus it is often avoided. Being the victim of a traumatic event and not being able to adapt, can be considered as a psychological or moral weakness, and could even constitute a stigma. It is not infrequent either that feelings of guilt arise, which makes it even more difficult for PTSD treatment.

In the biological response to a traumatic stressor, acute and chronic manifestations cause disorders of different body systems, which allow us to state that PTSD is considered a systemic pathology. In different groups studied, somatic comorbidities have been found with cardiovascular, gastrointestinal, and respiratory pathologies, with chronic pain, sleep disorders, obesity, metabolic syndrome, immunological disorders, and even accelerated aging. There is also a higher prevalence of risk factors such as high body mass index, and cigarette and alcohol consumption. All of these pathologies make PTSD treatment difficult, requiring comprehensive management.

As in other mental disorders, the spectrum concept has also been included in the area of psychotraumatology. With this approach, all the peritraumatic manifestations can be incorporated, from some initial isolated symptoms to the consolidation of a presentation of chronic progression. The different varieties of PTSD as acute/chronic, delayed appearance, simple/complex, hypervigilance/dissociated types, and its comorbidities: psychiatric (anxiety and depressive disorders, substance abuse, personality disorders among the most frequent) and medicine should allow for future development of constructs that hopefully will be more specific in the clinical as well as neurobiological aspects to be able to establish personalized treatments.

From the biological perspective it has been established that, while genetic molecular markers can give orientation in relation to the inheritance pattern to present a PTSD, a better indicator of the vulnerability to a peritraumatic response would be to provide phenotypes of traumatic stress spectrum and its genetic load.

One of today’s challenges is to establish the true prevalence of PTSD among immigrant, refugee, and asylum-seeker populations. Different study results show very variable figures (9% to 86%), but in general these are higher than the local population. We have to consider that risk factors and traumatic events can appear before, during, or after migration has occurred. Thus, future studies require representative and comparable sample sizes (including time of the study, reliability of translations for the interviews, and the different assessment instruments that are used, cultural and religious aspects, etc), to have more precise prevalences.

Another neurobiological aspect to consider is the trans-generational transmission of PTSD, which can be transferred from the mother, a victim of child abuse, to the child. Moog et al found that newborns from these mothers presented a smaller intracranial volume with
reduction in the cortex gray matter, which allows us to state that the consequences of child abuse can appear from intrauterine life onward.  

Finally, it is important to highlight the initiative from the Veterans Administration since 2014, a brain tissue bank of patients that had PTSD that facilitates biological research of this pathology.  

Conclusions

Considering the historical evolution of PTSD, from its first descriptions in soldiers to today’s definitions that include neurobiological variables and network analysis models, there is no doubt that it constitutes a diagnostic entity. PTSD can be considered a transversal diagnosis through different scenarios of the human activities. Nevertheless, it is a construct which is in full development conceptually, as well as in the challenge to clarify the different phenotypes that can be present.

The efforts of the neurosciences to discover the neuropathological mechanisms of psychological trauma, to identify biomarkers for vulnerability as well as for resilience, to isolate biological factors that allow the administration of specific drugs, and to be able to establish subgroups of PTSD and specific phenotypes associated with symptomatic profiles that today’s classification systems propose, constitute important challenges for research in this area.

The onset of PTSD in victims of traumatic events will depend upon the characteristics of the event and neurobiological and psychosocial risk factors. The critics of the construct, especially from socio-political perspectives, do not take away the validity of observations by clinicians and researchers of patients in medical settings as well as in the community.

As PTSD constitutes a public health issue, it is the physician’s responsibility to determine, with the diagnosis clinical rigorousness, and oversee that there is no overdiagnosis or underdiagnosis. PTSD as a psychobiological response to psychological trauma has, and will have, full validity in psychiatric nosology, independent of the name that is assigned to this syndrome.

Comorbidity in psychiatric diagnosis, as in somatic pathology, does not have to dampen PTSD diagnosis, but they are key factors to consider in treatment, since often these same aspects are the ones that make progression difficult and favor chronicity.

Controversies in relation to PTSD diagnosis in recent decades have been more a stimulus for research in different areas, than an obstacle for it. Patients, families, community, health care personnel, researchers, and society as a whole will always have something to say in relation to how a form of human suffering arises.

Today’s greatest challenge is constituted by the treatment of the individual patient that presents with PTSD. Interventions are very diverse and go from initial trauma management with psychological first aid, drugs that can potentially prevent the development of PTSD, diverse psychotherapies and pharmacological combinations for the acute onset, eye-movement desensitization and reprocessing therapy, brain stimulation, virtual reality, internet interventions, exercise, meditation, yoga and mindfulness, and even experimental drugs.

Finally, the clinician should choose the most adequate therapy for the individual patient and clinical guidelines, studies of meta-analysis, expert’s opinion, results of evidence-based clinical trials and other sources of therapeutic results as well as biological and psychosocial results which will be of use as the painter’s palette to design the therapy customized for the patient and strive to keep alive the art component in the exercise of medicine.

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The enormous successes in the genetics and genomics of many diseases have provided the basis for the advancement of precision medicine. Thus, the detection of genetic variants associated with neuropsychiatric disorders, as well as treatment outcome, has raised growing expectations that these findings could soon be translated into the clinic to improve diagnosis, the prediction of disease risk and individual response to drug therapy. In this article, we will provide an introduction to the search for genes involved in psychiatric illness and summarize the present findings in major psychiatric disorders. We will review the genetic variants in genes encoding drug metabolizing enzymes and specific drug targets which were found to be associated with variable drug response and severe side effects. We will evaluate the clinical translatability of these findings, whether there is currently any role for genetic testing and in this context, make valuable sources of information available to the clinician seeking guidance and advice in this rapidly developing field of psychiatric genetics.

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disease. The first-generation molecular genetic studies were, however, largely unsuccessful. Genetic linkage studies of psychiatric disease, pre-assuming existence of single major loci or few large-effect genes, produced mostly negative or irreproducible results. Candidate gene association studies primarily focusing on synthetic, degradative, and receptor components of neurotransmitter systems proved controversial.1,3

The release of a working draft of human genome sequence in 2000 marked the beginning of a new era, with enormous progress in the development of increasingly more efficient sequencing and genotyping technologies allowing the assessment of human genetic variation genome-wide, systematically, and much more completely. Exome- and genome-wide analysis in substantial numbers of individuals became feasible. Genome-wide association studies (GWAS) evolved as a key tool to identify genetic risk variants related to complex disease. This “reverse genetics” approach facilitated the identification of potentially pathogenic variants never previously conceived of, without prior pathophysiological hypothesis. Moreover, statistical methods were developed that allowed assessment of the aggregate effects of genome-wide DNA variation captured by GWAS,1 for instance by calculating the joint contribution of common variants as a “polygene score.”4 Finally, progress in psychiatric genetics would have been impossible without the international community combining data sets across multiple GWAS studies to maximize sample size (projecting for instance 100 000 cases for schizophrenia by 2019) and statistical power.5 So from 2011, replicated common SNPs began to emerge from the GWAS of major psychiatric disorders, beginning with schizophrenia6 and bipolar disorder.7 By far the strongest GWAS signal was the association between schizophrenia and genetic markers across the Major Histocompatibility Complex (MHC) locus on chromosome 6. Through very careful molecular dissection of this complex locus, the signal on chromosome 6 was traced to the C4 gene.8

It has been suggested that increased C4 activity in the brain of people with schizophrenia causes excessive synaptic pruning during postnatal brain development.8 If this is supported by further work, it is one of very few times that the underlying biological process has been revealed from a GWAS signal.

Mostly facilitated by data from high density genomic arrays used in GWAS, large de novo and rare chromosomal deletions and duplications, so-called copy number variants (CNVs), began to be identified, that substantially increase risk for psychiatric disorders, especially autism spectrum disorder9,10 and schizophrenia11,12 but also other conditions such as attention-deficit hyperactivity disorder (ADHD).13 Whole-exome sequencing (WES), the high throughput sequencing of all coding exons in the human genome, resulted in first (replicated) discoveries of de novo (gene-disrupting) coding mutations in autism spectrum disorder14-17 and schizophrenia.18,20

Taken together, the emerging architecture of psychiatric disease was found to be highly polygenic, with hundreds or even thousands of common variants of small effect size (with 1.1% to 1.2% absolute risk of illness compared with a ~1.0% population risk), accounting collectively for about one third to one half of the heritability between 0.4 and 0.8.2 Such a polygenic picture is typical for most complex traits. In addition, rare and de novo CNVs with large effect size (odds ratio ~2 to >20) as well as rare and de novo (disrupting) variants can significantly contribute to risk for major psychiatric disorders. The overall contribution of these types of variants is, however, less well understood.

There is increasing evidence for an etiological overlap between major psychiatric disorders, which would in many, though not all, instances have been predicted from their clinical presentation.2 Major psychiatric disorders have been found to share common genetic variation,5,21,22 with the first GWAS meta-analyses implicating neuronal/synaptic, immune and histone pathways.23 Similarly, an overlap has been observed for rare and de novo CNVs24 and other coding mutations.19,20 The substantial overlap of genetic risk between the disorders reinforces evidence for comorbidity from earlier genetic epidemiological studies, as exemplified by an increased risk for different psychiatric disorders in relatives of a patient.5 A recent, elegant study25 using transcriptomic profiling in the cerebral cortex across autism, schizophrenia, bipolar disorder, depression and

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**Selected abbreviations and acronyms**

<table>
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<th>Abbreviation</th>
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<tr>
<td>CNV</td>
<td>Copy number variant</td>
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<tr>
<td>OMIM</td>
<td>Online Inheritance in Man</td>
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<td>SNP</td>
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<td>SNV</td>
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alcoholism, revealed patterns of shared and distinct gene-expression perturbations across these disorders. Their data suggested that common polygenic variation underlies a substantial proportion of cross-disorder expression overlap. These results underscore that psychiatric disorders as “clinical-historical constructs” do not correspond to distinct definable pathophysiological entities and question the value of clinical diagnostic validity. Clinical utility refers to whether the disease phenotype or risks?). Replication is critical for correlation between the genetic variant and a specific genetic testing in psychiatry. Is time to address the potential clinical relevance of genetic testing in one form or another. Microdeletion 22q11.1 syndrome is typically caused by a recurrent 3 MB deletion of 40 genes, including Tbx1. Twenty to

Translating genetic findings to clinical practice

The enormous successes in genomic medicine, with the dramatic increase in the number of established gene-disease relationships for Mendelian disorders and the distinction of individual molecular tumor profiles in cancer allowing individualized diagnosis and treatment, have motivated efforts to advance precision medicine. These developments have been spurred mainly by the dramatic technological advances of the past 7 years with the implementation of next-generation sequencing (NGS) and all that it has enabled. Whereas genetic testing prior to NGS was performed primarily for very rare, single gene disorders, many of which had recurrent mutations, the advent of NGS has allowed the simultaneous interrogation of many genes and all their variants, using either targeted gene panels, WES, or whole genome sequencing (WGS). The detection of replicated genetic variants associated with neuropsychiatric disorders and treatment outcome has raised growing expectations that these results could be translated into the clinic, to improve individual diagnosis and the prediction of individual risk and treatment response, as well as predict the risk for other family members. Comprehensive genetic tests have become available, and are also commercially provided to doctors and individuals, not least by “direct-to-consumers” (DTC) testing. Thus, it is time to address the potential clinical relevance of genetic testing in psychiatry.

Prerequisites for genetic testing are analytic validity (does the test accurately detect whether a specific genetic variant is present or absent), and clinical validity (is there adequate scientific evidence to support the correlation between the genetic variant and a specific disease phenotype or risks?). Replication is critical for clinical validity. Clinical utility refers to whether the test can “provide information about diagnosis, treatment, management, or prevention of a disease that is likely to improve patient outcomes” (https://ispg.net/genetic-testing-statement/; http://www.cdc.gov/genomics/gtesting/ACCE/index.htm). The essential prerequisite is knowledge of the genetic causes of the disorder and robust genotype-phenotype correlations, to enable for instance predictive testing for later onset disorders for family members of affected patients.

As outlined above, major adult psychiatric disorders are generally not caused by a single gene or variant, nor do they have a rare Mendelian subform as many other complex disorders do, eg, the adult-onset neurodegenerative disorders such as Alzheimer disease. On the contrary, they are complex, highly polygenic disorders involving numerous genes and variants that have only a modest impact on risk and are neither necessary nor sufficient to cause disease. This makes a clinical interpretation of the present findings at the individual level extremely difficult, if not impossible. Thus, despite tremendous progress in recent years, psychiatric genetics has, with few exceptions, not yet sufficiently advanced to be able to deduce concrete recommendations, or even clinical guidelines, for the use of genetic testing for diagnostic purposes and risk prediction. This applies in particular to major psychiatric disorders which typically begin in adult life, such as depression, bipolar disorder, substance dependence, and schizophrenia (see also https://ispg.net/genetic-testing-statement/; the ‘Genetic Testing Statement’ of the International Society of Psychiatric Genetics (ISPG) is being periodically updated as research progresses).

There are, however, a few circumstances where genetic testing may be useful in various clinical settings. These pertain to the analysis of variants of strong effect, such as rare or de novo CNVs and disrupting mutations, prevalent in individuals with autism spectrum disorders (ASD), schizophrenia, or other psychiatric disorders, especially when accompanied by intellectual disability. ASD not only has shared phenotypic overlap with many syndromic forms, such as Down syndrome, Prader-Willi/Angelman syndrome and Fragile X-linked intellectual disability (about 4% to 5% of ASD), but is also one of the disorders for which rare variants have been demonstrated to have strong effect. The potential detection of such rare variants has made it amenable to genetic testing in one form or another. Microdeletion 22q11.1 syndrome is typically caused by a recurrent 3 MB deletion of 40 genes, including Tbx1. Twenty to
50% of patients with this deletion develop ASD,27 but the deletion is also found in approximately 1% of people with schizophrenia and also in patients with bipolar disorder and idiopathic Parkinson disease.28,29 Current microarrays detect an ASD-associated CNV in 7% to 10% of cases.30 There are now more than 50 ASD-associated CNVs and at least 61 ASD-risk genes, 18 of which have recently been identified in a comprehensive study using WGS of trios.31 Of the 61 ASD-associated genes, 36 (59%) are associated with known syndromes/phenotypes in OMIM (Online Mendelian Inheritance in Man, www.omim.org), with CHD8, SHANK2, and NLGN3 associated only with ASD. Many of the identified ASD-risk genes converge into shared biological pathways and networks, including synaptic and neuronal adhesion (SHANK3, SCN2A, GRIN2B, SYNGAP1, ANK2), axonal guidance, transcriptional regulation (eg, NFI, PTEN and SYNGAP1) and chromatin remodeling (eg, MECP2, MBD5, CHD8, ADNP, ARID1B and TBRI).31,32 Sixteen genes contain subdomains that could be targeted by pharmaceutical interventions and specific drug-gene interactions are known for seven genes.31 For example, individuals with pathogenic variants in SCN2A are potential candidates for drug trials involving allosteric modulators of GABA receptors.31

Multiple, rare CNVs have been associated with schizophrenia, all of which encompass many genes and are also common to other psychiatric and neurological disorders.33 Approximately 2.5% of schizophrenia patients will carry one of the associated CNVs, and many more genes may be associated through more powerful sequencing studies in the near future.35 The use of patient-parent trios to identify potentially harmful “de novo” variants has been applied to schizophrenia in a number of studies.18,20,36 Each of these studies demonstrated an excess of damaging de novo variants in schizophrenia, particularly in glutamatergic postsynaptic proteins and proteins whose messenger RNAs are targets of the Fragile X-linked mental retardation protein, FMRP. A subsequent, combined whole-exome sequencing case-control analysis in 4264 patients, 9343 controls and 1077 trios from previous studies revealed a significant excess of very rare, gene-disrupting variants in the SETD1A gene in patients (0.19%). This was the first statistically significant association between schizophrenia and a single candidate gene,37 although pathogenic SETD1A variants are also found in patients with more severe developmental and physical abnormalities. SETD1A is involved in histone methylation, substantiating the report that common risk variants for psychiatric disorders may aggregate on histone methylation pathways.23

Although individually rare, the net effects of CNVs across psychiatric disorders are substantial. Specifically, the net effects of the more frequent CNVs on a broad range of psychiatric and intellectual disability syndromes have already been sufficiently well-assessed by Malhotra et al38 and Gershon and Alliey-Rodriguez.39 A recent review of CNVs in schizophrenia in over 41 000 subjects by Marshall et al44 largely confirmed previous reports of CNV associations in schizophrenia, adding suggestive evidence for six novel CNVs and providing analyses of the genes involved and of the net effects of these CNVs on schizophrenia. Although the majority of adult patients would not be expected to carry a large CNV and such CNVs mostly lack diagnostic specificity, the identification of an inherited or de novo CNV in a known high-risk region for one of the major psychiatric disorders in such patients, may help diagnose a rare condition that has important medical and psychiatric implications for the patient and their family. Patients who carry such CNVs may find it easier to accept their diagnosis and adhere to treatment when presented with an objective “laboratory test.”39 Siblings and offspring could be offered genetic testing and might be reassured if they do not carry the same CNV as their mentally ill relative;39 (https://ispg.net/genetic-testing-statement/). The identification of de novo CNVs could be useful in the management of severe psychiatric disorders, especially those that present atypically or in the context of intellectual disability or certain medical syndromes (https://ispg.net/genetic-testing-statement/).

The analysis of genes involved in variable drug response

The pharmacological treatment of psychiatric disorders has been severely hampered by a large inter-individual variation in drug response and/or severe side effects, often leading to painful, frustrating and inefficient trial-and-error-based changes of treatment regimens. This variation is to a large extent due to genetic factors, with an estimated heritability h² of 0.6 – 0.8.40 Thus, numerous studies attempted to detect gene variants associated with individually different drug responsiveness or serious side effects. Their motivation was to iden-
tify pharmacogenetic biomarkers for drug efficacy and safety, which would allow prediction of an individual's response to drug therapy and facilitate individually tailored treatment. These studies focused primarily on the analysis of candidate genes including (i) genes involved in drug metabolism (pharmacokinetics); (ii) genes encoding the specific target molecules mediating drug action (pharmacodynamics); and (iii) genes mediating severe side effects. Typically, a few up to hundreds of SNPs within these genes were genotyped in cases and controls. Furthermore, GWAS were applied to scan the genome for variants predisposing to differential drug response “hypothesis-free,” allowing detection of yet unknown genes or biological mechanisms. In view of the immense literature, we will prioritize those results which proved to be most consistent and therefore merit further consideration for potential translation in the clinic. We will focus on the pharmacogenomics of antidepressants and antipsychotics. The results essentially refer to drug–gene relationships.

Two genes of central importance in the metabolism of antidepressants and antipsychotics are those encoding cytochrome P450 (CYP) monoxygenase system enzymes, CYP2D6 and CYP2C19. Variants in these genes can cause different pharmacokinetic phenotypes in individuals treated with the same dose of a drug: “ultrarapid metabolizers” (UM), characterized by significantly reduced drug concentrations, hence decreased drug effect or non-response; “extensive metabolizers” (EM) representing the “normal” phenotype; “intermediate metabolizers” (IM), characterized by drug concentrations that are higher compared to EM; and “poor metabolizers” (PM) having the highest drug concentrations at all, resulting potentially in drug-related toxicity due to overdosing. Thus, UM and PM appear to represent the clinically most relevant phenotypes/genotypes. In effect, comprehensive systematic literature reviews have substantiated evidence for lower plasma levels of antidepressants and antipsychotics in UM as well as an increased risk for non-response to tricyclic antidepressant treatment in UM as well as an increased risk for severe side effects in PM. The same applied to antidepressant treatment with selective serotonin reuptake inhibitors (SSRI). Regarding treatment with antipsychotics, the studies show a significantly increased risk for tardive dyskinesias in particular for CYP2D6-PM, while CYP2D6-UM overall does not appear to have a significant influence on antipsychotic drug response. Furthermore, a potential influence of CYP1A2 and CYP3A4 variants, other pharmacokinetic candidates of importance, on antipsychotic response has remained inconclusive. Importantly, the altered activity CYP2D6 variants have been reported to exhibit substantial population differences in comprehensive global surveys. Based on the first global data, Europeans showed the highest fraction of CYP2D6-PM (8%) and ~3% CYP2D6-UM, while for instance 40% of the population were CYP2D6-UM in North Africa. Thus, knowledge of ethnic background is of critical clinical relevance for the development of personalized pharmacological treatment strategies. The classification of pharmacokinetic phenotypes described above is subject to constant efforts towards further standardization. Although well-established, it does not yet represent the entirety of genetic variation, or allelic combinations. A meta-analysis of population scale sequencing projects integrating whole-genome and exome NGS data from 56,945 individuals of five major populations, demonstrated that the previous pharmacokinetic phenotype predictions from genotype data may have underestimated the prevalence of CYP2D6-PM and -IM subjects substantially. Between 25.3% and 70.3% of analyzed CYP alleles contained variant combinations with no or reduced functional activity. This trend was further substantiated in a comprehensive literature review. Another gene of potential importance for the pharmacogenetics of many antidepressants and some antipsychotics encodes the ATP Binding Cassette (ABC) Subfamily B Member 1 (ABCB1); this ABC transporter gene is expressed at blood-brain barrier (BBB) sites. Its membrane-associated gene product, P Glycoprotein, also known as Multidrug-Resistance Protein 1, transports various substances across the BBB out of the brain. Meta-analyses have shown associations of two (out of several) SNPs with antidepressant response. Overall, however, the role of genetic variation in ABCB1 in variable antidepressant response has remained controversial and will require further examination.

Concerning the analysis of pharmacodynamic candidate genes involved in antidepressant response, a large number of studies have addressed the gene encoding the serotonin transporter (SCL6A4), a direct target for most prescribed antidepressants. The functional insertion-deletion polymorphism located in the promoter region, 5-HTTLPR, possibly was the most studied variant in relation to antidepressant response at all. Significant associations between this polymorphism and antidepressant
response and remission rates were described in major meta-analyses. Particularly, a higher probability of response and remission to SSRI treatment was observed in Caucasian carriers of the long (“l”) allele, although its influence on SSRI efficacy was of modest effect. Inversely, Caucasian patients with the short (“s”) allele were found to have difficulties to achieve remission and showed a reduced response to SSRI as well as an increased risk for side effects. Overall, however, the results are still inconsistent, precluding the use of 5-HTTLPR as a predictor of antidepressant response at present. Condensing other candidate gene data of note, a comprehensive meta-analysis has suggested a significant association of variants in the serotonin 2A receptor gene (HTR2A) with antidepressant response; the same was true for variants in the gene encoding the FK506-binding protein 5 (FKBP5), which is involved in the regulation of stress hormones. Furthermore, this meta-analysis substantiated evidence that heterozygous carriers of the rs6265 polymorphism (Val66Met) in the brain-derived neurotrophic factor gene (BDNF) respond best to SSRI, particularly Asian patients. Numerous other plausible candidate genes have been investigated, with controversial results and modest effect sizes overall.

Concerning pharmacodynamic candidate genes involved in antipsychotic treatment response, the most consistent results have been obtained for genes of the dopaminergic and serotonergic systems. Thus, an insertion deletion (Ins/Del) polymorphism of the dopamine D2 receptor gene (DRD2) was found significantly associated with antipsychotic drug response, Del allele carriers exhibiting a poorer response rate than patients with the Ins/Ins genotype. Moreover, a Ser9Gly polymorphism of the dopamine D3 receptor gene (DRD3) showed a consistent, though not significant trend for the Ser-allele and reduced clozapine response. Also, two polymorphisms in the HTR2A gene (His452Tyr and T102C) were found associated with clozapine response. Another receptor gene of the serotonergic system (HTR2C) contained a C759T polymorphism, the C-allele of which conferred a significantly increased risk for antipsychotic-induced weight gain, one of the most consistent associations observed in antipsychotics. Strong candidates known to be involved in the genetics of obesity, the melanocortin 4 receptor (MC4R) and leptin genes, were also suggested to be prominent risk factors predisposing to this serious adverse effect of antipsychotics. Finally, several polymorphisms of the HLA-system, specifically HLA-B38, DR4 and DQw30 and HLA-DQB1 and HLA-B61 were found associated with clozapine-induced agranulocytosis, another serious side effect of antipsychotics. For a detailed summary of the genetics of common antipsychotic-induced adverse effects see also MacNeil and Müller. Numerous studies were performed with candidate genes potentially involved in lithium response, which all were inconclusive, in part also due to its unresolved underlying biology.

Translating pharmacogenomics to clinical practice

Pharmacogenomic studies aimed to improve individual psychiatric drug treatment through pre-emptive genotyping, which would allow adjustment of dosages to reduce the risk of overdosing and serious side effects, or a change of drug. In sum, the scientific evidence to support the clinical validity of pharmacogenetic testing is still insufficient for most gene-drug pairs. Moreover, the clinical utility of specific gene-drug pairs has not yet been clearly demonstrated in adequately powered, double-blind clinical trials, which need to be conducted to clarify whether patients benefit substantially from genotype-guided treatment compared to “treatment as usual.” Also other factors that influence treatment response such as co-medication, age, gender, disease symptoms/comorbidity, smoking and diet and, importantly, ethnic background, need to be taken into account and studied further. Despite these limitations, CYP2D6 and CYP2C19 testing has already been recommended for clinical use, and guidelines for using and generating genetic information have been outlined. First implementation studies using CYP2D6 and CYP2C19 genotype information in clinical practice indicated that pharmacogenetic testing was very well accepted by both physicians and patients, could particularly be beneficial for non-extensive metabolizing patients, and hold great potential for optimization of drug treatment in psychiatry. Recently, the Individualized Medicine: Pharmacogenetics Assessment and Clinical Treatment (IMPACT) study was launched to demonstrate the feasibility and utility of pharmacogenetic testing on a large scale and facilitate implementation of this testing in routine health care practice. The implementation of pharmacogenomics in the clinic is supported by the establishment of comprehen-
sive resources such as the Pharmacogenomic Knowledge Base (PharmGKB) (https://www.pharmgkb.org), and international expert groups that enable objective and transparent assessment of existing pharmacogenetic studies to derive clinical recommendations, such as the Clinical Pharmacogenomics Implementation Consortium (CPIC). Accordingly, CPIC performs a systematic review/evaluation of the comprehensive literature curated in PharmGKB to develop peer-reviewed gene–drug guidelines that are published and updated periodically (for further information on pharmacogenetic resources see Pouget et al40 and Müller et al).42 Thus, CPIC guidelines for CYP2D6 and CYP2C19 genotype-directed dosing of tricyclic antidepressants as well as SSRIs44,46 have been published. These guidelines provide concrete information for the interpretation of genetic tests, that is, a list of existing genotypes with their “likely (pharmacokinetic) phenotypes” assigned and corresponding dosing recommendations or alternative therapeutic recommendations (suggesting selection of a drug not primarily metabolized by CYP2D6). The expert groups’ recommendations are further translated by national or cross-national regulatory agencies. Thus, the US Food and Drug Administration (FDA) and other agencies distinguish for instance four categories, “required,” “recommended,” “actionable,” and “informative,” this classification of gene-drug pairs often varying between agencies and countries.

In sum, there is very good consensus concerning the pharmacogenetic testing of CYP2D6, which is “recommended” for therapy with tricyclic antidepressants with particular reference to the increased risk for serious side effects in patients with PM-status. Also the testing of CYP2C19 is considered “particularly clinically relevant.” Beyond avoiding harm, testing both CYPs is considered to improve therapy through selection of alternative drugs and provide useful information for many other diseases. Agencies such as the FDA have begun to include pharmacogenomics information in drug labeling and recommend genetic testing for now 25 psychiatric drugs.42 As emphasized in the Genetic Testing Statement released by the ISPG, clinicians are encouraged to consider such recommendations in their treatment decisions and to “stay current on changes to drug labeling and adverse event reports” (https://ispg.net/genetic-testing-statement/). The FDA and other agencies “require” genetic testing in patients of Asian ancestry before carbamazepine treatment; carriers of the major histocompatibility allele HLA-B*15:02 are at highly increased risk to develop Stevens-Johnson syndrome (SJS), a potentially lethal skin disease. The only other “required” genetic test concerns children and adult patients who receive pimozide, an antipsychotic, to prevent side effects in CYP2D6-PM.

Conclusions and outlook

Psychiatric genetics has generated very promising results in terms of risk variants associated with major psychiatric disorders and treatment outcome. Despite these successes, psychiatry still lags behind other fields in medicine in terms of translation of existing knowledge into diagnostic genetic tests that could facilitate early diagnosis and accurate classification of disorders. The nature of genotype-phenotype-relationships has remained largely elusive, and the “fundamental biology” of psychiatric disorders has yet to be revealed.1,5 Significant progress can be expected from several lines of technological advancement/development. For example, there is reason to be excited about the prospect of WGS being increasingly implemented as the assay of choice for both gene discovery and diagnostic testing in highly heterogeneous disorders. Advantages of WGS include its comprehensiveness, with the analysis of coding and non-coding sequence, the improved coverage of sequences, and in fact, of whole genes that were previously not easily sequenced, as well as the detection of all types of genetic variation. This also promises to increase diagnostic yield. Moreover, it will allow establishment of a catalogue of non-coding variation, which is assumed to contribute substantially to the development of psychiatric disorders. One could envisage a comprehensive, genome-wide panel assay, where one assesses all known variants with proven associations to psychiatric disorders in an individual patient. Since these disorders, as well as individual drug response, are complex traits which can be influenced by multiple genes, further progress can be expected through assessment of gene-gene interactions, gene networks and the application of systems approaches.67 Complex traits are also significantly influenced by environmental factors. Thus, the analysis of the epigenome as the interface between genome and environment is expected to contribute key insights into the development of psychiatric disorders.68,69 True genome-wide assessments of epigenetic marks, such as
DNA methylation, or chromatin modifications have become possible, mainly also through progress in second-generation DNA sequencing methods. Furthermore, the inaccessibility of the human brain can now be overcome by stem cell approaches, which make it possible to study (pluripotent stem cell-derived) neurons from patients “in a dish.” The generation of CNS organoids as model systems may open new avenues towards precision drug treatment. Beyond technological advancements, a reconsideration/rethinking of previous research concepts could critically move the field forward. As outlined by Kapur et al., to achieve clinical utility of diagnostic genetic testing may require a new approach. Rather than comparing prototypic patients to healthy controls, the field should focus on “identifying biologically homogeneous subtypes that cut across phenotypic diagnosis.” Validating such biomarker/genetically-defined subtypes will require longitudinal studies of individual patients, providing the “natural basis for a ‘stratified’ psychiatry that will improve clinical outcomes across conventional diagnostic boundaries,” ultimately more compatible with the major goal of precision medicine—and the findings obtained to date.

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Introduction

Brain imaging was more broadly introduced into neuroscience and the field of mental disorders in 1976, when ventricular enlargement was described in patients with multi-episode schizophrenia compared with controls. Subsequently, a wide range of structural and functional brain imaging studies were performed that provided a plethora of findings in different brain disorders. To provide a manageable review of this data, this paper focuses on structural imaging in patients with Alzheimer disease, bipolar disorder, major depressive disorder (MDD), and schizophrenia; it thereby goes beyond the use of these data to exclude underlying brain diseases such as tumors and vascular and inflammatory conditions and discusses other applications.

The first successes in the attempts to identify structural imaging markers to support diagnostic, prognostic, and therapeutic processes are likely to be in Alzheimer disease because it is a classical neurodegenerative disorder with an established neuropathological basis. The search for such markers in so-called affective and non-affective psychoses, namely bipolar disorder, MDD, and schizophrenia has not yet led to reliable markers. The present paper will discuss recent findings in the field of structural brain imaging and their clinical implications.
schizophrenia, is likely to take longer because these disorders lack an established neuropathological basis. It appears that a much greater number of brain imaging studies will be needed in these disorders to identify a common neurobiological basis in each of them.

The first section summarizes the state of the art of structural imaging findings in the above mentioned mental disorders and the second section outlines the future role of structural brain imaging in predicting diagnosis, outcome, and therapy.

State of the art of the clinical usefulness of brain imaging in mental disorders

Alzheimer disease

Alzheimer disease has been known for over one hundred years to be a progressive neurodegenerative disorder with a defined neuropathological basis. Large-scale epidemiological studies have convincingly shown that the disease process starts decades before the clinical manifestation of the disorder. This fact has fuelled many brain imaging studies to identify patients at risk of developing dementia.

Although medial temporal lobe volume loss seen in magnetic resonance imaging (MRI) is not specific for Alzheimer disease, the differential pattern of brain-wide atrophy separates patients with pathologically confirmed Alzheimer disease from healthy controls (sensitivity 97%, specificity 94%)\(^2\,3\) and from patients with dementias with other underlying pathological changes, such as frontotemporal lobe degeneration and Lewy body disease (sensitivity 91%, specificity 84%)\(^4\,5\).

Stephan et al\(^6\) performed a large population-based cohort study to try to predict dementia in individuals aged older than 65. Brain MRI scans were performed a mean of 4.2 months after the baseline examination with a 1.5 Tesla Magnetom. Interestingly, the study found no significant differences in the discrimination performance of white matter lesion volume, brain volume, hippocampal volume, or all three variables combined. However, the inclusion of hippocampal volume alone or all three MRI variables in a conventional risk model that included cognitive, lifestyle, and genetic predictors, among others, significantly improved reclassification of risk and showed increased benefits in the decision curve analysis (a measure of the value of the prediction model).\(^6\) A combination of functional imaging (positron emission tomography, PET) and structural imaging (MRI) best predicted conversion when PET signals were increased in posterior medial and lateral cortical regions, \(^18\)F-fluorodeoxyglucose (FDG) PET signals were increased in medial temporal and temporal basal regions and gray matter volume was decreased in medial basal and lateral temporal regions.\(^3\) This finding indicates the benefit of including PET studies in diagnostic assessments. However, a Cochrane review on nine studies on \(^11\)C-Pittsburgh compound B PET (\(^11\)C-PIB-PET, a compound that makes amyloid depositions visible in the living human brain) could not demonstrate the usefulness of this type of PET.\(^7\) The review included 274 participants with any accepted definition of mild cognitive impairment (MCI) at baseline and found that 112 participants subsequently developed Alzheimer disease, equating to a conversion rate of 35%. For every hundred \(^11\)C-PIB-PET scans, one person with a negative scan progressed to Alzheimer disease, whereas 28 people with a positive scan actually showed no progression. The authors concluded that “we cannot recommend \(^11\)C-BIP-PETs for routine use in clinical practice.”\(^7\)

In a more recent systematic review based on 29 papers on amyloid imaging, 23 papers on FDG-PET and 8 papers on both techniques, both amyloid and FDG-PET qualified as suitable biomarkers for the diagnosis of Alzheimer disease.\(^8\) Although the authors concluded that both techniques detect Alzheimer disease with high sensitivity and specificity compared with other neurodegenerative processes and cognitively normal, aged-matched individuals, they recommended further studies with standardized conditions and a lengthier longitudinal follow-up. Furthermore, to establish these two techniques as state-of-the-art biomarkers for clinical practice they recommended studies to validate the link between these imaging techniques and the neuropathological diagnosis, rather than just the clinical diagnosis. The authors noted that biomarkers such as these are urgently needed to identify subgroups of patients with Alzheimer disease in whom disease-modifying drugs can be tested and later used successfully. This approach is based on the assumption that in the near future the underlying pathophysiological mechanisms of such subgroups will be better understood, leading to the development of targeted treatment options.

In summary, hippocampal volume as determined from structural MRI is an established parameter to support the diagnosis of Alzheimer disease and its at-risk
states. FDG-PET and amyloid PET are on their way to qualifying as biomarkers to identify persons at an increased risk to develop Alzheimer disease and thus require specific treatment.

**Bipolar disorders**

Bipolar disorders, in particular bipolar I disorder, are clinically characterized by manic and depressive phases. The prevailing hypothesis is that dysfunctional catecholaminergic systems and inflammatory processes play a role in the pathophysiology, at least in a subgroup of patients. Furthermore, there is increasing evidence from basic science that glial and microglial processes are involved.9

Considering that only about 35% of patients with bipolar I disorder,10,11 it is interesting that there are only a few consistent brain imaging findings in this disorder. A meta-analysis of individuals with bipolar I disorder (n=321) only found an increase in the volume of the left temporal lobe, right putamen, and right lateral ventricle compared with healthy individuals (n=442).12 It found no significant differences between bipolar patients and healthy controls in any other brain regions. These findings are supported by a recent MRI analysis by the ENIGMA bipolar working group.13 Taking the influence of lithium treatment into account, the group found that patients with bipolar disorder treated with lithium had a larger mean total, left and right hippocampal volumes and total, left, and right amygdala volumes than patients not treated with lithium and healthy individuals. Global cerebral volume also differed significantly between the groups in that patients with bipolar disorder not taking lithium had a smaller mean volume than both healthy individuals and patients with bipolar disorder taking lithium. All bipolar patients, regardless of lithium use, had larger total and left temporal lobe volumes than the healthy individuals, although after correction for multiple testing only the findings for the left temporal lobe remained significant. With regard to the current discussion on the influence of antipsychotic treatment on brain structure, it is interesting to note that this study found no difference in any regional brain volume between those patients taking antipsychotic medication and those not taking such medication.12

Structural MRI machine-learning paradigms seem to be helpful when attempting to distinguish patients with bipolar I disorder from patients with schizophrenia. One study used the gray matter density images of 66 schizophrenia patients, 66 patients with bipolar I disorder, and 66 healthy individuals to train three support vector machines to separate patients with schizophrenia from both healthy individuals and patients with bipolar disorder and patients with bipolar disorder from healthy individuals.14 The predictive power of the models was tested by cross-validation and in an independent validation set of 46 patients with schizophrenia, 47 patients with bipolar disorder, and 43 healthy individuals scanned on a 3T MRI scanner. The patients with schizophrenia could be separated from the healthy individuals with an average accuracy of 90% and from the patients with bipolar disorder with an average accuracy of 88%.14 The model was less accurate for the patients with bipolar disorder and correctly classified 67% of the healthy individuals and only 53% of the patients with bipolar disorder. All in all, these results show that gray matter pathology shows a unique pattern in schizophrenia and bipolar disorder and can thus help to reliably differentiate between these disease groups by using machine-learning paradigms. In another study that assessed structural and resting-state functional MRI data from 21 patients with bipolar disorder, 25 patients with unipolar depression, and 23 healthy controls, a linear support vector machine with a forward-backward search strategy classification of bipolar and unipolar depression achieved an accuracy of 92%.15

In summary, patients with bipolar I disorder show a specific pattern of brain abnormalities in structural imaging in the temporal lobe, basal ganglia, and ventricular system. In addition, cortical abnormalities are prominent enough to allow bipolar disorder to be distinguished from schizophrenia with the help of machine learning.

**Major depressive disorder**

Depressive illness is characterized by phases of significantly depressed mood and lack of drive, lasting at least 2 weeks. Besides these two main symptoms, other symptoms include sleep disturbances, cognitive dysfunction, weight problems, and other features. The most common hypothesis for the pathophysiology of Major Depressive Disorder (MDD) suggests disturbed serotonergic and noradrenergic subsystems caused by a dysbalance of neuroplastic processes related to the stress axis.16 In short, MDD is a stress-related disorder that is sensitive to acute stressors, especially environmental ones.
Gray matter volume deficits reported in voxel-based morphometry (VBM) studies in MDD have been found in frontotemporal regions, the anterior cingulate cortex, and the occipital gyrus, among others. After antidepressant treatment in this study, patients still had gray matter volume reductions in the dorsal anterior insula, cingulate cortex, and superior frontal gyrus.

In the quest to identify prognostic subgroups of patients with depression, one interesting line of evidence is based on structural brain imaging in late-life depression (LLD) and its treatment-resistant variant. LLD has been associated with global cerebral atrophy, decreased myelin integrity, and lesions in frontostriatal-limbic regions. In particular, the association with cerebral lesions in frontostriatal-limbic areas helps to explain the “depression-executive dysfunction syndrome” observed in LLD and supports cerebrovascular burden as a pathogenic mechanism. In a similar line, in LLD regional atrophy is associated with treatment outcome; in particular, hippocampal volume reduction is found in patients showing an unfavorable outcome. An increased number of white-matter hyperintensities (WMH load) and diminished white-matter functional anisotropy are also associated with poor therapeutic outcome in LLD. In summary, the vascular burden as defined by regional volume reduction, WMH load, and disturbed white-matter integrity seems to represent the common ground for an increased risk of LLD and an unfavorable treatment outcome in this subgroup of patients. Brain imaging and especially structural methods clearly help to distinguish this prognostic subgroup of depression. Novel treatment options are needed to target this subgroup of “vascular depression” and the “executive dysfunction-depressive syndrome.”

By targeting treatment-refractory depression in general, one study was able to use gray matter volume in structural MRI to predict individuals with treatment-resistant depression compared with healthy controls with 85% accuracy. By using an automated feature selection method, the authors found that the major brain regions supporting this significant classification were the caudate, insula, habenula, and periventricular gray matter.

Finally, a learning method called alternating decision trees provided the most accurate prediction models for diagnosis of LLD (87% accuracy) and treatment response (89% accuracy). The authors suggested that combining multi-modal imaging with non-imaging measures may help to better predict LLD diagnosis and treatment response.

In summary, imaging can be used as a kind of biomarker in attempts to define the usefulness of structural brain imaging in MDD and in particular non-response in LLD. The subgroup of patients with LLD can be defined on the basis of structural brain imaging because of their common pathophysiology, described as increased vascular load. Identifying the key vascular mechanisms for the development of LLD might pave the way to unraveling the pathophysiology of this subgroup of patients and identifying new treatment approaches.

**Schizophrenia**

Schizophrenia is a severe mental disorder characterized by illness episodes with positive symptoms, such as delusions and acoustic hallucinations, and/or negative symptoms, such as lack of drive and cognitive disturbances. Because of the success of treatment with dopamine blocking agents, schizophrenia is regarded as a disorder of disturbed dopaminergic transmission. If one looks further downstream in the neurobiological cascade, this group of illnesses can be regarded as a disturbance of the regenerative capacities of the human brain and to a lesser extent, a disturbance of inflammatory processes. For quite some time, however, schizophrenia was regarded as a consequence of a classical degenerative process that resulted in an unfavorable long-term functional outcome in the majority of cases.

Thus, the interest in unravelling the neurobiological basis of schizophrenia has a long and distinctive history that is rooted in neuropathology and is accompanied by a plethora of structural brain imaging literature, starting in 1976 with the first computer tomography (CT) study in schizophrenia. Meanwhile, large-scale studies have been performed, such as those by the ENIGMA consortium that assessed 2018 patients with schizophrenia and 2540 healthy controls at 15 centers worldwide and used a meta-analytic approach. Compared with healthy controls, patients with schizophrenia had smaller hippocampus, amygdala, thalamus, nucleus accumens, and intracranial volumes and larger pallidum and lateral ventricle volumes. The putamen and pallidum volume enlargements were positively associated with illness duration (length of treatment) and hippocampal volume deficits were more severe in those samples that had a higher proportion of unmedicated patients.
Another meta-analysis and critical review of studies involving structural MRI techniques in patients with psychosis selected 80 studies published between 1976 and 2015 and searched for biomarkers for schizophrenia. The authors concluded that, despite having data from structural brain imaging studies on psychosis from over 40 years, they could not identify a diagnostic or prognostic biomarker for clinical use. According to the authors, this lack of clinical usefulness of neuroimaging on psychosis was due to small samples, unclear biomarker definitions, and a lack of replications. In their literature search, the authors did identify one study, however, that meets advanced criteria for biomarker detection. The study used machine-learning methods and neuroanatomical-based biomarkers and was able to differentiate schizophrenia from mood disorders early in the course of the illness. Therefore, the currently unsuccessful search for simple regional or global neuroanatomical measures that are unequivocally associated with psychosis might turn into progress with the help of more advanced analytical methods, such as machine learning. For example, these methods have helped to develop neuroanatomical biomarkers to predict progression from prodromal psychosis to first-episode schizophrenia and the response to treatment and to predict symptomatic outcome or functional outcome. However, the very promising predictive results, ie, for the short- and long-term outcome in first-episode psychosis, need to be replicated in independent samples. A reliable prediction of 80% or more might not be achieved when the same predictive biomarkers are used in an independent replication sample.

In conclusion, in the past 40 years a substantial number of structural brain imaging studies have been published on schizophrenia. They have helped to identify a pattern of structural abnormalities (in particular in hippocampus, amygdala, thalamus, nucleus accumbens, intracranial, pallidum, and lateral ventricle volumes) that differ from Alzheimer disease and other psychotic illnesses such as MDD and bipolar disorder. However, because no regional or global neuroanatomical measure has been unequivocally associated with psychosis, new analytical methods need to be implemented to progress the field. Machine learning might be one such method that can support the development of biomarkers to aid diagnosis, prognosis, and treatment outcome.

Future directions: biomarkers for prediction

Diagnosis

Since the introduction of structural brain imaging methods into clinical practice, researchers have been promising that these methods will aid diagnosis, outcome, and therapy. In daily clinical practice, structural imaging does help to identify organic disorders such as tumors, infarction, or inflammatory processes that cause or exacerbate the symptomatology in mental disorders. This is certainly helpful because it allows a small subgroup of patients to be identified and treated, eg, by the neurosurgical removal of a tumor, who otherwise may not have been diagnosed correctly; in such cases, a thorough psychiatric and neurological workup may not indicate an underlying organic cause and, consequently, the use of structural imaging might be life-saving. A study in 656 patients with schizophrenia and 722 healthy controls, however, found clinically relevant pathology in only 11.1% of the patients and 11.8% of the controls. None of the neuropathological findings observed in the patients was interpreted as a possible substrate for organic psychosis. This study suggested that MRI scans do not need to be an essential part of routine screening in psychotic patients. This conclusion was accepted by the National Institute of Health and Care Excellence (NICE) and included in the current version of their guidelines on schizophrenia.

Irrespective of the role of structural imaging in clinical routine the question arises whether structural imaging is useful in patients with mental disorders, beyond excluding organic brain disease. In Alzheimer disease, studies have convincingly shown that hippocampal volume reduction, as determined with structural MRI, helps to establish the diagnosis and independently identifies individuals at an increased risk of developing the disease. The hippocampus volumes assessed in structural images can be combined with other parameters from cerebral spinal fluid, neuropsychology, and functional imaging (FDG-PET, amyloid PET) to increase the predictive value. In this way, structural imaging complements the clinical diagnosis of Alzheimer disease with a number of biomarkers that allow a diagnostic certainty of up to 90% in cases later verified by neuropathological examinations.
In psychotic disorders such as MDD, bipolar disorder, and schizophrenia, the search for biomarkers to support the diagnostic process seems to be more difficult than in Alzheimer disease. In MDD, structural imaging helps to define a distinctive subgroup, namely LLD, and more specifically its treatment-resistant variant. Moreover, taking hippocampal volume, the load of white matter intensities, and white matter integrity into account might help to define this relevant subgroup of MDD and thus to establish specific therapeutic possibilities for it.

The application of machine learning as a new analytical approach has allowed structural imaging to be reliably used in the early phases of psychosis to distinguish between patients with schizophrenia and those with MDD. Beyond this, machine learning has allowed “converters” from prodromal to first-episode schizophrenia to be identified with an accuracy of more than 80%. This rate was achieved not only at single study centres such as university hospitals in Munich, Germany, and Basel, Switzerland, but also at a network of several centres. Currently, the large PRONIA study (www.pronia.eu) is attempting to replicate these findings on a Europe-wide level. If successful, this study may show that structural imaging can help to identify people with prodromal psychosis who are in need of intensive care and treatment to prevent conversion.

Outcome

In addition to the need for biomarkers to aid diagnosis eg, for Alzheimer disease or psychosis, there is an even greater need for biomarkers to help identify relevant subgroups of patients with regard to their short- and long-term outcome. Much of the success in oncology stems from the development of biomarkers that identify subgroups of patients with a specific pathophysiology who can then be given targeted treatment. Along these lines, a study was able to use clinical data to predict functional outcome at 4 weeks and 1 year in patients with first-episode schizophrenia. Retrospectively, machine learning enabled the identification of patients with a functional outcome above and below a Global Assessment of Functioning (GAF) score of 65. If replicated in a prospective fashion (eg, in OPTiMiSE), this finding would help to identify different prognostic subgroups of schizophrenia and improve pathophysiological understanding, ideally leading to more specific treatment options.

Therapy

Combining real-time functional MRI with neurofeedback can help to improve treatment in psychiatry. Besides functional MRI other metabolic neurofeedback instruments, such as near-infrared spectroscopy, have become potential therapeutic tools. MRI neurofeedback has been shown to be effective in schizophrenia, in both emotion regulation and alcohol abuse. In summary, the use of functional imaging to complement structural imaging in the development of “theranostic” biomarkers is a promising area.

Conclusion

The current review examines the clinical usefulness of structural brain imaging in Alzheimer disease, MDD, bipolar disorder, and schizophrenia. Besides identifying underlying organic brain pathologies (eg, brain tumors and vascular or inflammatory processes), structural brain imaging can support diagnostic processes in Alzheimer disease. When used together with machine learning and related analytical methods, structural imaging allows patients with schizophrenia to be distinguished from patients with depression in the early phases of psychotic illness. Besides these diagnostic markers, biomarkers of short- and long-term outcome are needed to establish prognostic subgroups of mental disorders, as has been achieved in oncology, for example. Such biomarkers will help to identify subgroups of patients with a distinct pathophysiology and to develop more specific treatment options. The use of real-time functional MRI in neurofeedback has developed into a very useful “theranostic” biomarker to increase therapeutic success.

As a final point, one must note that despite the frequent use of the term “biomarker” in this paper, the development of clinically useful biomarkers for mental disorders is a tedious process that follows a defined pathway and requires large samples for replication and verification.

In conclusion, a number of mostly uncontrolled studies have shown that structural brain imaging is needed to exclude organic brain disorder after the initial clinical diagnosis in Alzheimer disease, depression, bipolar disorder, and schizophrenia. This application is not completely undisputed, however, eg, in schizophrenia. A recent large-scale study comparing patients with
schizophrenia with healthy controls identified no excess of brain pathology in the patient group that would explain the psychotic symptomatology. This finding was taken by NICE as a lack of evidence for including brain imaging methods in the diagnostic process and included as such in its recent schizophrenia guideline. However, in our opinion it is premature to claim that brain imaging methods are not useful and at least one other prospective, well-controlled study is needed to draw such a conclusion. Beyond this, studies with new biostatistical methods, such as machine learning, have provided evidence that structural imaging allows us to predict the risk for developing the illness, identify prognostic subgroups, and determine the efficacy of treatments in mental disorders, in particular schizophrenia. In schizophrenia, brain imaging parameters predict the risk to develop the illness with a good probability of 0.75 and above, help to distinguish between affective and nonaffective psychoses, and identify groups with a good or fair outcome. Currently, well-controlled prospective studies are trying to replicate these initial findings. If they do so, there will be little doubt that structural brain imaging is clinically useful to exclude organic brain disorder and that it may serve as a biomarker for diagnosis, prognosis and treatment.

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REFERENCES


Is there a role for reproductive steroids in the etiology and treatment of affective disorders?

David R. Rubinow, MD; Peter J. Schmidt, MD

Introduction

The idea of using hormones to treat affective illness is by no means novel. In 1849, Berthold suggested that animal organs (testes) contained substances that could, upon exogenous administration (through transplant), dramatically alter physiology (including behavior). The field of organotherapy was subsequently born with the publication of a paper in The Lancet in 1889 by Claude Edouard Brown-Sequard. This paper reported that the subcutaneous self-administration (by the author) of extracts of ground-up dog and guinea pig testes reversed many of the effects of aging and had a profoundly salutary effect on energy and mood (all of which was likely a substantial placebo response). Although most of the reports from this field over the next 30 years were subsequently refuted (as most, but not all, organ extracts are inactive when orally administered), the benefits associated with the administration of thyroid extract and adrenal extract for their respected deficiency syndromes (myxedema...

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and Addison’s disease) were substantiated and gave rise to the modern field of endocrinology.

Although the enthusiasm for organotherapy gradually disappeared in the early 20th century, the belief that one could treat behavioral disorders with “hormones” (a term coined in 1905) was substantially bolstered following the isolation and characterization of estradiol in 1929. Werner (1934) performed a placebo-controlled trial of an estradiol preparation, “theelin,” in involutional melancholia and demonstrated theelin’s superior efficacy. During this period, many reproductive steroids were isolated and characterized including estrone, progesterone, and several androgens. Further, chemists identified modifications of the steroids that could alter their absorption (ie, acetylation) and potency (eg, addition of ethynyl group or removal of C-19 methyl groups), thus fueling a renewed interest in reproductive steroids as medicines. In the 1950s menopausal symptoms were treated with estrogen replacement therapy, and 1960 saw FDA approval of the first oral contraceptive (ie, Enovid). Hormone therapy “took off” (albeit with the trajectory of a rollercoaster rather than a rocket), and papers appeared describing the use of reproductive steroids in affective disorders related to reproduction: involutional melancholia, premenstrual syndrome, and postpartum depression. In this article, we will not comprehensively review hormonal therapy but rather will focus on reproductive steroids in women to attempt to answer the following questions: How do hormones work and what accounts for the variability in response to hormones? How do hormones affect the systems implicated in depression? How can new models of depression help us to understand the role of reproductive steroids in affective regulation? What is the evidence for a role of reproductive steroids in affective illness? What is the therapeutic role of reproductive steroids in the treatment of depression? The concepts that will be developed apply to men and women and can be summarized as follows: i) the effects of hormones on the brain are pleiotropic and highly context dependent; ii) the paucity of well-designed studies and methodologic shortcomings preclude certainty about the role of hormones in the treatment of affective disorders; iii) one can, nonetheless, define a role for hormones in reproductive endocrine-related mood disorders in women that help answer what is perhaps the critical question in psychiatry, namely why do people respond differently to ostensibly the same stimulus?

How do hormones work and what accounts for the variability in their actions?

The original meaning of hormone—a glandular secretion that is distributed by the bloodstream to distant sites—is, for our purposes, woefully inadequate. Hormones include small (peptides) and long proteins as well as steroids, which act at membrane and intracellular receptors as well as ion channels, act at time frames from seconds to hours, can be synthesized de novo in non-glandular tissues like the brain, and can be synthesized in neuronal terminals and released into synapses to effect post-synaptic cellular activation. To reduce the scope of our discussion to manageable dimensions, we will focus on one class of hormones, ovarian steroids. All steroid hormones (including non-ovarian steroids) are metabolized from cholesterol. Cholesterol is transported into the mitochondria by STAR (steroid acute regulatory hormone) and then metabolized to pregnenolone, which gives rise to all of the biologically active steroids through a series of enzymatic steps performed by a small group of enzymes with multiple actions along the steroid synthetic cascade. As such, the way in which a steroid is metabolized determines its action. Testosterone can be aromatized to estradiol, which then activates the estrogen signaling system, can be reduced to dihydrotestosterone, an androgen 2-10 fold more powerful than testosterone, or can be metabolized to androsterone, a “neurosteroid” that can acutely regulate membrane neurotransmitter receptors. Classical steroid signaling involves intracytoplasmic receptors (although some principally reside in the nucleus), which are bound by the steroids after they diffuse through the cell membrane. The receptors are transcription factors, which recruit other proteins to form a complex that remodels chromatin (to make genes accessible for the messenger RNA (mRNA) transcribing enzyme, RNA polymerase) and recruits the transcription factors that help initiate transcription. Steroid receptors can also join with other transcription factors—a process called tethering—to initiate transcription of genes that do not have classical receptor binding sites—response elements—in the DNA. Through these combined mechanisms, steroids can regulate thousands of genes. Additionally, steroid receptors exist at the membrane, from which they can initiate downstream signaling to activate enzymes, amplify the effect of activated receptors, or di-
rectly influence transcription. Finally, steroids like estradiol regulate the activity of all three polymerases (ie, those generating mRNA, ribosomal RNA, and transfer RNA), thus allowing estradiol to prepare cells acutely for transcription and more chronically for translation (protein formation).

The variability of steroid actions is best conveyed by the array of protein partners with which they combine to achieve a biological outcome. For example, there are approximately 350 coregulatory proteins—both coactivators and coinhibitors—that bind to hormone bound steroid receptors to determine whether genes are turned on or off. As described by Lonard and O’Malley, these coregulators (TS) combine in groups, and the impact of each of the coregulators is determined by its chemical modification (eg, phosphorylation, methylation). With even only eight potential modifications of each coregulator and groups of six, there are 10^13 different potential functional outcomes of a hormone-bound receptor! Further, coregulators exist in a tissue-specific fashion, enabling estrogen-like compounds called SERMs (selective estrogen receptor modulators) to act like an estrogen agonist in some tissues and an antagonist in others, depending on the coregulator profile in the cells. Further contributing to the signaling variability, the effects of steroids are highly context dependent, with that context including prior exposure and genetic background.

How do hormones influence the systems implicated in depression?

Given the protean effects of steroids, it should not be surprising to learn that virtually every system implicated in depression is modulated by estradiol. The following are just three examples (see refs 13 and 14 for more complete discussion):

1. Neurotransmitter “deficiency.” The synthetic and metabolic enzymes and receptors for all classical neurotransmitters are regulated by estradiol. Estradiol also primes neurons to respond more efficiently to stimuli, in part through regulation of the brain’s major excitatory neurotransmitter, glutamate. Through the two major estrogen receptors, ER α and β, estradiol can activate metabotropic (indirectly linked to ion channels) glutamate receptors even in the absence of glutamate and increase the synaptic trafficking of at least one type of ionotropic (ion channel containing) glutamate receptor, the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor. Estradiol also directly regulates the activity of calcium and potassium channels, thus acutely (in seconds to minutes) regulating neuronal excitation, inhibition and neurosecretory coupling. If depression is a consequence of excitatory/inhibitory imbalance, estradiol is in a prime position to modulate that disturbance.

2. Neuroplasticity deficiency. Estradiol promotes neuronal survival, decreases oxidative stress, improves neuronal energetics by increasing mitochondrial respiratory efficiency, increases both dendritic spine density and synaptic plasticity, and increases cell survival in response to a variety of toxic insults (eg, hypoxia, inflammation, excess glutamate, decreased glucose). Levels of brain-derived neurotrophic factor (BDNF), a critical growth factor deficient in depression, is increased by estradiol, just as it is by antidepressants.

3. Network abnormality. Neural networks are structurally and dynamically connected brain regions whose coordinated activity enables effective and efficient responses to the environment. Examples of neural networks include the following: a) The Default Mode Network, which mediates internal-based thought (eg, day dreaming, reflecting) and permits recall of the past and imagining of the future; b) Social Cognition Network, which enables one to “read” the intentions of others (theory of mind); c) Reward Network, which permits the assignment of affective valence (positive or negative) to events, thoughts, and experiences and is critical for decision-making; d) Affective Regulation Network, which regulates the interplay between more cognitive (eg, dorsolateral prefrontal cortex [dlPFC]) and more “affective” (eg, limbic, amygdala) brain regions; e) Central Executive Network, critical for mediating executive functions like cognitive appraisal. Evidence exists for dysfunction of each of these networks (and others) in depression. Similarly, evidence exists for the modulation of these networks by estradiol. For example imaging studies performed in women whose reproductive state was manipulated by administering the gonadotropin-releasing hormone agonist leuprolide (which suppresses ovarian steroid secretion) alone or in combination with estradiol or progesterone demonstrated that estradiol,
but not progesterone, activated key regions of the DMN (medial PFC and posterior cingulate; Wei et al, unpublished data): both estradiol and progesterone supported the top-down modulation of the hippocampus by the dlPFC (affective regulation network), coordinated/coupled activity that was absent during hormone suppression. In a recent animal study, McHenry et al described a hypothalamic reward circuit that was powerfully regulated by estradiol. Both estrus cycle and exogenous estradiol resulted in a dramatic, in vivo upregulation of self-administered optogenetic stimulation to genetically defined medial preoptic neurons, with the estradiol-induced reward behavior linked to activation of the ventral tegmental area and phasic dopamine release in the “reward center” (nucleus accumbens).

How can new models of depression help us to understand the role of reproductive steroids in affective regulation?

One can argue that depression represents an “adaptive failure;” ie, a failure of integration or orchestration of neural networks that subserve the functions observed to be disturbed in depression. As such, depression represents a dynamic or “software” problem, not a “hardware” problem. Just as there is no single gene abnormality in depression, there is likely no single brain region “lesion” in this disorder, with the “focus” of dysfunction dynamically shifting across time. In line with this view, depression is not a collection of particular symptoms so much as it is a dysregulation of affective state. What is a state? A state can be defined as a transient, coherent, replicable, integrated, self-organized assemblage of thoughts, associations, affects, memories, perceptions, interpretations, etc. States are programs for interpreting and interacting with our environment in an efficient fashion. For example, the cognitive/affective/perceptual/behavioral state that might accompany a picnic on a beautiful day would clearly not be in evidence if you were suddenly attacked by a bear. The advantage of the state model is several-fold. First, it overlays nicely on the network model, permitting both the formation and changes in state to be described in terms of component network functions and dynamic interactions between networks. Second, it allows us to focus on the kinetics of affective state change rather than simply the particular set of symptoms. Depression, then, can be thought of as the failure to be able to change affective state, which otherwise should be both transient and susceptible to either our environment or our efforts to modify our state. Indeed, Bunney et al suggested 50 years ago that depression might best be understood by studying the characteristics of the switch rather than the characteristics of the depressed state. Consistent with this suggestion, premenstrual dysphoric disorder (PMDD) should be seen not as a collection of specific symptoms but as an affective state change that is choreographed by the menstrual cycle. Third, the state model is testable; ie, if one hypothesizes that reproductive steroids are informational molecules that “by design” generate behavioral states, then one should be able to alter the appearance of distressing affective states in reproductive endocrine-related mood disorders by manipulating the reproductive context in which the disorders appear (as will be described below).

What is the evidence for a role of reproductive steroids in affective illness?

Conceptually, the most promising affective disorders in which to search for a role of reproductive steroids are those that are temporally linked to periods of reproductive endocrine change: perimenopausal depression (PMD), postpartum depression (PPD), and PMDD. None of these disorders is characterized by abnormal levels of reproductive (or any other) hormones, so clearly these are not endocrinopathies like hypothyroidism. Several studies suggest that PMD can be effectively treated with estradiol, but that says nothing about the role of estradiol in the precipitation of the affective state. Schmidt et al addressed this question by determining whether the blinded withdrawal of estrogen therapy in euthymic women with a history of PMD would precipitate a switch into a depressed state. The blinded withdrawal of estradiol did indeed precipitate a dysphoric affective state within one week, before the appearance of withdrawal-related hot flushes. Notably, the same hormone manipulation procedure was completely without effect on affective state in women lacking a history of PMD. This study, therefore, suggested that withdrawal of estradiol would precipitate a depressed state, but only in those who were, for unclear reasons, susceptible (ie, those with a history of perimenopausal depression). A second endocrine manipulation paradigm created a scaled-down model of the puerperium.
in euthymic women with a history of PPD. In this case, it was the addback of high-dose reproductive steroids that precipitated the switch into the depressed state. Once again, however, the identical hormone manipulation paradigm in women without a history of PPD produced no affective state change at all. (These findings have recently been replicated in a larger group (Schiller et al, manuscript in preparation.) Finally, in PMDD, the experimental and blinded elimination of the mid-late luteal phase of the menstrual cycle did not influence the appearance of the PMDD state, which emerged in the experimentally created follicular phase, thus uncoupling PMDD from the endocrine events of the mid-late luteal phase. In a subsequent study, ovarian suppression did prevent the appearance of the PMDD state, which was then precipitated under blinded conditions by the addition (in the context of ovarian suppression) of estradiol or progesterone. As the same hormone manipulation was without effect on women without a history of PMDD, the findings suggested that the reproductive steroids did precipitate the PMDD state, but only in those who were, again, differentially sensitive to the effects of the steroids. As one can observe in Figure 1, it was impossible to determine whether the change in steroid levels following their reintroduction was the offending stimulus or whether the hormones simply played a permissive role in the expression of an infradian zeitgeber (which would be consistent with the attenuation of the steroid-precipitated affective state despite continued hormone administration). As recently described (Figure 2), a hormone manipulation study involving blinded administration of 12 weeks of estradiol and progesterone administration in the context of ovarian suppression demonstrated that it was the change (ie, increase) in hormones that triggered the depressed state, which then gradually attenuated without subsequent appearance throughout the remainder of the 12 weeks. Together, these findings are most consistent with a role of reproductive steroids in regulating the appearance of a dysfunctional affective state (in a susceptible group) rather than simply “making patients symptomatic.”

Although the source of the susceptibility is currently unknown, the hormone manipulation paradigm described above (ovarian suppression + hormone add-back) was exploited to identify a group of women with PMDD in whom the critical variable of hormone sensitivity was confirmed, as was its absence in the comparison group. Lymphoblastoid cell cultures were then created and transcriptomics performed (by RNAseq in the first group and by qRT-PCR in the replication sample). Among the gene “families” identified as differentially expressed in the pathway analysis, the ESC/E(Z) family was selected for further study for the following reasons: i) it has only 13 member genes; ii) it is regulated by estradiol and progesterone; iii) it has been implicated in affective disorders; and iv) it is a major mediator of epigenesis, the process by which the environment can regulate, in an enduring fashion, the expression of genes. Almost all of the 13 genes in this family were upregulated in the cells from the women with PMDD (in both samples), four significantly so. Further, and most interestingly, the response of four of these genes to exposure to estradiol or progesterone in culture for 24 hours differed in patients and controls. These data provide the first demonstration of a cellular model for the differential sensitivity to reproductive steroids that characterizes women with reproductive endocrine-related mood disorders. In the implication of a major epigenetic regulatory system, they also provide a plausible model for how a normal (internal) environmental signal (ie, reproductive steroids)—one critical for long-term potentiation and synaptic rewiring—might acquire the capacity to trigger a switch into a state characterized by network dyscoordination.

What is the therapeutic role of reproductive steroids in the treatment of depression?

The unfortunate answer to this question, despite all that we have learned about the dramatic role of reproductive steroids in the regulation of affective state, is that we simply don’t know. In a 1997 meta-analysis, Zweifel and O’Brien described a reasonably impressive effect size of 0.68 for the effect of hormone replacement therapy (HRT—estrogen plus a progestin) on depression. This suggested that HRT might be a promising treatment for or prophylaxis against depression. In a recent systematic review of studies examining the effects of HRT or estrogen therapy (ET) on mood in menopausal women since the 1997 meta-analysis, there was a remarkable paucity of well-designed, well-controlled randomized clinical trials (RCTs). Just some among the myriad methodological problems are as follows: i) menopausal state was not defined or represented a mixture of perimenopausal and
Figure 1. Recurrence of sadness in women with premenstrual syndrome during estradiol or progesterone add-back in the context of GnRH agonist-induced ovarian suppression. Ten women with premenstrual syndrome and 15 control women had minimal mood symptoms while receiving leuprolide acetate (a GnRH agonist). In contrast, the women with premenstrual syndrome but not the controls had a significant increase in sadness during the administration of either estradiol or progesterone. Values are the means (SE) of the seven daily scores on the sadness scale of the Daily Rating Form for each of the 8 weeks preceding hormone replacement (leuprolide alone) and during the 4 weeks of estradiol (plus leuprolide) and progesterone (plus leuprolide) replacement. A score of 1 indicates that the symptom was not present, and a score of 6 indicates that it was present in the extreme. \( P = 0.003 \) for interaction of treatment condition, diagnostic group, and week.

Figure 2. Upper Panel: Plasma estradiol (A) and progesterone (B) were significantly increased in the three months of estradiol/progesterone add-back compared with the last month of leuprolide and the month of single-blind placebo. There were no significant differences in plasma levels between the first month of estradiol/progesterone add-back compared with the second and third months of estradiol/progesterone add-back. Lower Panel: The pattern of between month differences in symptom severity reflects the presence of significantly increased Premenstrual Tension-self (C) and –rater (D) scores during the first month of estradiol/progesterone add-back (Month 5) compared with all other months (ie, last month of leuprolide alone, placebo, and the second and third months of estradiol/progesterone add-back). In contrast, there were no significant differences in symptom severity scores in either Premenstrual Tension-self or –rater scores between the last month of leuprolide alone (Month 3) and scores during placebo, second and third month of estradiol/progesterone addback. Finally, Premenstrual Tension scores in the second and third months of estradiol/progesterone add-back also were not significantly different.

postmenopausal women, despite the markedly different physiologic characteristics of these two groups; ii) antidepressant effects were inferred from a group that was not depressed at baseline; iii) depressive symptoms from a rating scale were not distinguished from depression, a syndromal diagnosis; iv) important covariates (eg, past history of depression, presence of hot flushes) were not examined or reported; and v) risk of bias was moderate to high in almost all studies. Of the hundreds of studies reviewed, only 24 met criteria, and only five RCTs clearly examined depressed women! Based on three RCTs, one of the conclusions reached was that estradiol may have antidepressant efficacy in perimenopausal but not postmenopausal depressed women. This conclusion mirrors the “critical window” hypothesis by which (primarily) beneficial effects are attributed to hormone therapy initiated proximate to, but not distal from, the end of ovarian activity. This hypothesis, which finds both support and explanations in the animal literature was adduced by some to explain the surprising results of the Women’s Health Initiative (WHI) Study. This massive study was intended to test the effects of HRT on coronary heart disease (CHD) (primary outcome) and breast cancer (primary adverse outcome). Contrary to the 50% decrease in CHD with HRT seen in many observational studies, the WHI found a significant, 29% increase in CHD. The expected increase in breast cancer (found in observational studies with more than 4 years of HRT) was also found, and the study was terminated early in 2002. This study was heralded as the end of HRT, and indeed subsequent research on the effects of estradiol in humans almost disappeared. Criticisms of the WHI methodology appeared almost immediately, and among the legion concerns (eg, use of medroxyprogesterone acetate, which has many adverse physiologic effects; poor health of large numbers of participants), one of the most prominent was the observation that the mean age of subjects was 63.3 and only 15% of subjects were within 5 years of the menopause. In other words, the critical window was ignored by the very design of the WHI. In subsequent reanalysis of the WHI data, the adverse cardiovascular effects were not observed in those between the ages of 50 and 59 or in those receiving only estradiol, thus confirming earlier objections to the WHI.

The lost opportunity to investigate the psychotropic efficacy of estradiol in the wake of the WHI has no doubt limited the extent and reliability of the conclusions that can be drawn regarding the use of estradiol in affective disorders. Suggested conclusions are the following: i) In perimenopausal (not post-menopausal) women who are depressed and have other perimenopausal symptoms (eg, hot flushes, vaginal dryness), it is reasonable to initiate estradiol treatment before starting an antidepressant (as perimenopausal symptoms are a clearly agreed upon indication for estrogen therapy); ii) Perimenopausal depressed women who refuse to take (or are intolerant of) psychotropics may be tried on estradiol; iii) There is little theoretical or practical justification for using estrogen to treat depressed women who are more than several years post menopause; iv) Any woman started on estradiol should have a gynecologic and breast exam; additionally one should familiarize oneself with potential contraindications (eg, multiple family members with a history of breast cancer, family history of premenopausal or bilateral breast cancer, past history of breast cancer or thromboembolic disease including stroke); v) the effects of hormone therapy will depend on the type (ie, estrogen with or without progestin), dose, route, formulation, and duration; estradiol, particularly transdermal, is recommended, as it is least likely to be associated with thromboembolic phenomena and best recapitulates the premenopausal profile of estrogen metabolites. vi) Although one could consider the use of estradiol as an adjunct in perimenopausal women unresponsive to antidepressant therapy, available data are particularly exiguous and do not permit conclusion regarding the efficacy of this approach. To end on a somewhat more optimistic note, Gordon et al recently reported a prospective study of the prophylactic effects of 100 ug/day of transdermal estradiol compared with placebo over 1 year in 172 euthymic, perimenopausal women. The women receiving estradiol were significantly less likely to experience clinically significant depressive symptoms during the study (CES-D>16, OR=2.5), with the mood benefits particularly prominent in proportion to the number of significantly stressful life events in the 6 months prior to study initiation (ie, the greater the number of stressful life events, the greater the prophylactic benefit of estradiol). These findings suggest that with time and additional study, the proper place for reproductive steroids in the treatment of affective state dysregulation may well be better defined.
Conclusions and future directions

Undeniably, reproductive hormones can regulate mood, and their manipulation can, in specific instances, dramatically alter the course and expression of affective illness. Nonetheless, these hormonal effects are not universal and instead appear in subgroups of individuals who are differentially sensitive to the impact of reproductive steroids on the central nervous system. Going forward, it will be critical to identify the mediators of this differential sensitivity, facilitating the prediction of those who would respond to reproductive therapies and, of equal importance, those who might be at risk for adverse effects. Additionally, the very complexity of steroid actions that precludes simple inference about potential psychotrophic mechanisms of action offers tremendous opportunity for “designer psychopharmacology,” whether through specific hormone preparations or receptor agonists/antagonists, steroidogenic enzyme inhibitors, or selective hormone receptor modulators (capitalizing on tissue-specific coregulators). Current uncertainties notwithstanding, the future for reproductive hormone therapy is deservedly bright.

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It is widely believed that suicide prevention involves the consideration of risk and protective factors and related interventions. Preventative interventions can be classified as “universal” (targeting whole populations), “selective” (targeting higher-risk groups), and “indicated” (protecting individuals). This review explores the range of preventative measures that might be used commensurately with different types of suicide prediction. The author concludes that the best prospects for suicide prevention lie in universal prevention strategies. While risk assessments do generate some information about future suicide, suicide risk categorization results in an unacceptably high false positive rate, misses many fatalities, and therefore, is unable to usefully guide prevention strategies. The assessment of suicidal patients should focus on contemporaneous factors and the needs of the patient, rather than probabilistic notions of suicide risk.

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the strength of the suicide predictions is considered using the statistical metrics of sensitivity (the proportion of all suicide cases included in the higher-risk group), discrimination (effect size distinguishing the probability of suicide in higher and lower suicide risk groups), and the positive predictive value (the probability that patient in a higher-risk group will die by suicide). Only once these metrics have been established can the question be asked–exactly what type and how much prevention is suitable in light of a suicide prediction? For example a burdensome or inconvenient targeted intervention, even if highly effective against suicide, can only be commensurate with a prediction that carries a high positive predictive value, such that only few people will suffer unwarranted consequences. Similarly, a selective intervention that advantages a higher-risk group can only be commensurate with a degree of discrimination between lower-risk and higher-risk groups if it does not unfairly disadvantage the lower-risk group that miss out on the intervention.

**Prediction and prevention at a national level**

Worldwide in 2015, about 788,000 people died by suicide at a global rate of 10.7 per 100,000 person-years (or about 1 in 9,350 people per annum). That year, national suicide rates were lowest in the small Caribbean nations of Antigua and Barbuda, Barbados and Grenada, each of which had suicide rates below 1 per 100,000 person-years among populations of fewer than a quarter of a million. However, in 2015, suicide rates also varied remarkably between populous nations, ranging from 1.4 per 100,000 person-years in Jamaica to 34.6 per 100,000 person-years in Sri Lanka (Table II). While some of this international variation might be a result of differences in the definition suicide or methods of data collection, there is little doubt that there are large and real differences in national suicide rates. Decades of work standardizing the reporting of suicide has not resulted in converging rates, and national suicide rates are notably stable on a year-to-year basis. Hence, suicide rates between nations can vary by more than an order of magnitude. This suggests that some preventative measures might be justified in nations that have a higher suicide rate, but not in lower suicide rate nations. For example, although two nations might have similar problems with agricultural pests, the overall benefit of restricting access to toxic pesticides might clear in high suicide rate countries like Sri Lanka (where 1 in 2900 die by suicide each year) but might be less obvious in low suicide rate countries like Jamaica (where as few as 1 in 74,500 die by suicide each year).

The reasons for the marked heterogeneity in international suicide rates are not fully understood. One important observation is that national suicide rates by particular lethal methods (such as hanging, poisoning,

<table>
<thead>
<tr>
<th>Example of a group with a predicted increased rate of suicide</th>
<th>Approximate increased odds of suicide (measure of discrimination)</th>
<th>Approximate absolute risk (Equivalent of positive predictive value)</th>
<th>The proportion of all suicides identified (Equivalent of Sensitivity)</th>
<th>Example of a possible preventative strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>National group – Sri Lanka 2015²</td>
<td>About three times the global suicide rate</td>
<td>1 in 2900 per year</td>
<td>All national suicides</td>
<td>Universal preventative measures such as the restriction on pesticides</td>
</tr>
<tr>
<td>Demographic group – men in the USA 2015³</td>
<td>Men had over three and half times the suicide rate of women</td>
<td>1 in 5100 per year</td>
<td>About 75% of all suicides</td>
<td>Reducing men’s access to firearms</td>
</tr>
<tr>
<td>Diagnostic group – Schizophrenia²⁷, ⁷⁰</td>
<td>About a ten-fold risk</td>
<td>1 in 20 lifetime risk</td>
<td>About 5% of all suicides</td>
<td>Earlier treatment of psychosis and clozapine</td>
</tr>
<tr>
<td>Level of psychiatric care – Recently discharged psychiatric patients²⁷, ⁷⁰</td>
<td>About a 100-fold risk compared to the general population</td>
<td>1 in 4000 in the first three months post discharge</td>
<td>About 5% of all suicides</td>
<td>Higher proportion of patients followed up post discharge</td>
</tr>
<tr>
<td>Higher-risk psychiatric patients²⁹</td>
<td>About a five-fold risk</td>
<td>1 in 18 over 5 years</td>
<td>56% of all patient suicides</td>
<td>Not clear</td>
</tr>
<tr>
<td>Individual suicide risk</td>
<td>Not known</td>
<td>Not known</td>
<td>Likely to be small</td>
<td>Hospitalization?</td>
</tr>
</tbody>
</table>

Table I. Examples of predictive groups, measures of suicide risk, and possible preventative strategies.
gassing, shooting, jumping, and drowning) vary greatly between nations but tend to be stable within nations on a year-to-year basis. This predictability of method-specific suicide rates underpins most universal measures to prevent suicide. Well-known examples include the substitution of natural for coal gas in the United Kingdom in the 1960s, the regulation of firearms in Australia in the 1990s, and the trend towards bans on highly hazardous pesticides in many countries. Each of these universal measures resulted in reductions in both cause specific suicide mortality and a drop in suicide rates. Other universal preventative measures are the reduction in analgesic pack size, the substitution of barbiturates with benzodiazepines, the placement of barriers at jumping hotspots, measures to decrease alcohol consumption, and changes to media reporting of suicides. In each of these cases (with the slightly contentious exception of the regulations in firearms) suicides rates have been reduced at little or no cost or inconvenience to the whole population.

Some potential universal prevention strategies come at a greater cost. Examples include, better access to health care and measures to reduce unemployment. Other universal, potentially important measures might be inexpensive but hard to achieve, for example reducing suicide by reducing the stigma associated with accessing mental health care.

Despite the challenges faced by nations with a high suicide rate, universal measures hold the best hope for global suicide prevention. To illustrate, if global suicide rates were similar to those of Jamaica, Indonesia, or Pakistan, suicide would fall from its current place in the top 20 causes of death to about the hundredth cause of global death.

**Prediction and prevention according to demography**

In addition to heterogeneity in suicide rates between nations, major differences in suicide rates can be found according to demographic characteristics within national populations. Selective prevention strategies based on the higher suicide risk of a demographic group are based on the assumption that any inconvenience caused by a prevention strategy can be borne by all members of the risk group and that its benefits should be denied those outside the group. While this may seem common sense, it can lead to perverse outcomes.

Consider the example of the male sex. Being a man is undoubtedly the most prevalent global risk factor for suicide. Worldwide, more than twice as many men than women suicide, and in high-income countries rates of male suicide are often three times female rates. In many countries, the male sex can be considered to have a sensitivity for suicide of about 70% (because 70% of all suicide victims are male) and male sex discriminates for future suicide with much the same or greater effect size as suicidal thoughts and behaviors (that typically confer an increased odds over those without suicidal thoughts and behaviors of about two).
though the positive predictive value of suicide according to mental disorder is over 90%. Mental disorder is also quite a strong discriminator of suicide risk. One meta-analysis found that compared to the general population, those with major depression have a twenty-fold risk of suicide, while those with bipolar disorder, eight-fold for schizophrenia, and seven-fold for personality disorders.

The positive predictive value associated with lifetime suicide in mental disorder is far from trivial, estimated to be over 5% for schizophrenia, 4% for those hospitalized with affective disorders, and over 2% for never hospitalized people with an affective disorder.

The strength of the association between mental disorder and suicide suggests that the treatment of mental disorder might be an efficacious way of preventing suicide. However, the view that suicide can be prevented simply by the treatment of mental disorder is both overly simplistic and overly optimistic. Sadly, the evidence for the suicide preventing properties of psychological therapies and medical psychiatric treatment is less strong than might be generally believed. Recent meta-analyses of the mortality in trials of commonly prescribed antidepressants have failed to demonstrate a protective effect against suicide. Similarly there is little evidence for the suicide-reducing effects of antipsychotics or electroconvulsive therapy.

There is some evidence that clozapine can reduce suicide risk in schizophrenia and that lithium is protective against suicide in major mood disorders, but it is doubtful whether suicide prevention afforded by these treatments alone can justify their serious side effects. This is not to say that antidepressants, antipsychotics, and mood stabilizers should not be prescribed for suicidal patients—but the benefits of a medication and its effectiveness in suicide prevention are not always closely related. The symptoms of depression, schizophrenia, and bipolar disorders are often well-controlled by these medications and their prescription is easily justified, irrespective of any perception of suicide risk. Moreover, some treatments for mental disorder are used ethically even if they increase the risk of suicide. Benzodiazepines are an evidence-based treatment for alcohol withdrawal and some anxiety states but are associated with an increased suicide risk, likely because of their disinhibiting effects and toxicity in overdose.

## Prediction and prevention according to levels of psychiatric care

The higher levels of psychiatric care provided in emergency departments and by psychiatric hospitalization have recently emerged as important suicide risk factors that offer plausible opportunities suicide prevention. In the modern era of psychiatric deinstitutionalization suicide rates among currently psychiatrically hospitalized people are typically about 50 times community suicide rates, rising to an astonishing 100-fold risk dur-
ing the 3 months after discharge.\(^\text{31}\) This suggests that a current or recent psychiatric admission is the strongest known discriminator for suicide. Viewed through the lens of a predictive test, about 20% of all suicides are previously hospitalized patients (sensitivity)\(^\text{38}\) and the long-term suicide risk of hospitalized patients (positive predictive value) has been reported to be 2.5% for men and 1.5% for women.\(^\text{42}\)

Current and former inpatients are a well-defined group who might benefit from selective suicide preventative measures. While the absolute risk of suicide associated with inpatient care might not justify prolonged hospitalization or other restrictions on liberty,\(^\text{43}\) some less intrusive suicide preventative measures seem to be quite effective. In the United Kingdom, inpatient suicide rates have declined in response to a range of measures including the reduction in hanging points\(^\text{44}\) and by policies for regular observation in hospital.\(^\text{45}\) Moreover, reducing the stigma and trauma associated with psychiatric admissions might prevent some suicides.\(^\text{46, 47}\)

**Prediction and prevention using higher-risk categories**

Suicide risk assessment is widely recommended in clinical practice\(^\text{48-51}\) and often has the explicit aim of creating suicide risk groups denoted by the terms high, medium- and low-risk.\(^\text{52,53}\) While there is no agreement about how to perform a suicide risk assessment, inquiring about suicidal thought and behaviors is usually considered central to the task.\(^\text{54,55}\) Specialist mental health services often insist on semi-structured risk assessment using lists of risk factors, and some researchers advocate for suicide risk questionnaires or scales.\(^\text{56}\) Each of these approaches meets this paper’s definition of prediction as a method that can identify groups or individuals at increased risk of suicide.

A 2017 review examined the predictive properties of suicide risk assessment quantified by recent meta-analyses.\(^\text{57}\) The review located meta-analyses that found that no risk factor,\(^\text{58}\) or combination of risk factors,\(^\text{59}\) was so strongly associated with suicide as to be clinically useful. One meta-analysis found that the positive predictive value of suicidal ideation for suicide was about 1% per annum,\(^\text{60}\) while a second found that higher-risk categorizations based on multiple risk factors discriminated between higher-risk and lower-risk groups with pooled odds of 4.84 and a sensitivity of 56%.\(^\text{59}\) Two meta-analyses calculated the positive predictive value among “higher-risk” patients to be 5% in the long-term.\(^\text{59, 61}\)

These replicated, robust, and ultimately disappointing results suggest that while risk assessments do provide some information about future suicide, this information is limited and a very limited set of selective suicide-preventing interventions might be rationally used on the basis of a higher-risk categorization. If as few as 5% of higher-risk people die by suicide in the long term, any commensurate suicide reducing intervention must be both benign and cost-effective so as to be acceptable to the remaining 95%. Furthermore, if such a benign and cost-effective long-term or long-lasting intervention were available, there would be very strong arguments that the same intervention should be offered to lower-risk patients, among whom over 40% of suicides occur.

**Prediction and prevention of suicide by individual patients**

Suicide risk assessment aims to reduce the uncertainty about future suicide. So far I have assumed that this uncertainty is statistical in nature and that it can be measured using metrics of sensitivity, discrimination, and positive predictive value. However, uncertainty is often regarded as having two components, the first component resulting from chance factors, is variously denoted as statistical, probabilistic, or aleatory uncertainty and the second component being epistemic, resulting from a lack of knowledge.\(^\text{52-64}\) Both types of uncertainty are at play in medical practice. For example, an intravenous drug user is at increased probability of contracting human immunodeficiency virus—but on presentation with an opportunistic infection, whether he or she has acquired immunodeficiency syndrome is not a matter of chance but of facts that can be resolved by increased knowledge, in this case by performing blood tests.

There is little doubt that aleatory factors play a major role in suicide. The potential range of future events experienced by people is large and unknowable. Further, the degree of complexity of a person’s biology, psychology and social setting strongly points to the role of non-linear dynamics, rendering suicide unpredictable even if all the initial risk and protective factors could be known.\(^\text{65}\) However, here I would like to briefly consider whether increased knowledge of an individual person can meaningfully reduce uncertainty about suicide to the point of indicating measures to prevent an
individual suicide. On initial consideration this seems unlikely because the law of large numbers dictates that uncertainty in a single trial is always greater than the uncertainty of repeated trials and because of the empirical evidence that statistical or actuarial approaches are generally better at forecasting human behavior than clinical judgment.66

However, in some circumstances clinicians might come to a high degree of certainty on epistemic grounds. Consider the example of a young, employed, non-mentally ill, and never psychiatrically admitted mother who was found to have written a suicide note before taking a deliberate and well-planned overdose of a highly lethal substance. The lack of many established suicide risk factors and the protective factor of children suggest a lower suicide risk, but epistemic knowledge of the details of the suicide attempt and of the circumstances described by the patient might lead a clinician to make a judgment that the patient is suicidal. In practice this sort of epistemic judgments might not be rare.

Two questions then arise. How reliable are epistemic assessment of future suicide and what might be rationally done to prevent suicide in the event of an epistemic judgment of imminent suicide?

The answer to the first question is not known. What is known is that nomothetic risk factors (risk factors possessed by classes or cohorts of individuals), including the presence of suicidal thoughts and behaviors, alone cannot lead to certainty about suicide. If judgments about suicide are to reach a very high level of certainty this can only be achieved with specific, proximal, and idiographic factors (those that are unique to the individual) and not with what are traditionally considered to be risk or protective factors. Moreover, this has to be a contemporaneous judgment (given the weakness of predictive algorithms) involving as little in the way of forecasting as possible. This is not to say that this form of certainty is not sometimes possible, but it does imply that clinicians should examine the evidence before them very carefully, and that they should give less weight to traditional risk factors when making judgments about suicidality than is generally held.

Assuming that a clinician has formed the view that the patient is suicidal, what then is the appropriate preventative step? The most common response is that the patient should be observed and protected until their distress has resolved. This observation and protection often involves admission of the patient to a psychiatric hospital. While it is generally assumed that hospitalization can prevent suicide, this has never been demonstrated empirically. Moreover, there is a minority view that the loss of autonomy, trauma, and stigma associated with hospitalization contributes to suicides in the inpatient and setting47 and in the post-discharge period.67

How the limits of suicide prediction impact on prevention

The limits of suicide prediction appear to be profound. The single strongest discriminator of suicide risk is status as a current or recent psychiatric hospital patient, and this association is more than an order of magnitude stronger than the degree of discrimination made possible by other forms of suicide risk assessment.

In the future some improvement in risk assessment might flow from the identification of hereto-unknown risk factors68 or by new ways of combining established risk factors, such as with machine learning69 and other methods derived from nonlinear dynamics.65 However new methods of suicide risk assessment might only be useful if they have powers of statistical discrimination greatly exceeding existing methods.

There may also be a role of real-time monitoring using new wearable technologies. However, even if proximal measures obtained by real-time monitoring do have a much stronger discrimination between suicide and non-suicide than conventional risk factors, the positive predictive power will not be increased and may even be lower because of the intrinsically low base rate of suicide over short time frames.

Moreover, the limitations of prevention also impact on the usefulness of suicide prediction. There is simply no value in a prediction that cannot lead to an effective preventative measure. While the positive predictive value can be assumed to be a relevant factor in judgments about ethics of exposing false positive cases to adverse effects of suicide preventing interventions, the effectiveness of the interventions is also relevant. Despite the widespread adoption of suicide risk assessment there are no published randomized tri- als demonstrating that risk assessment can guide any suicide-reducing interventions to the point of reducing the overall prevalence of suicide in the assessed group, and it remains to be seen if this evidence threshold can be achieved by any new suicide-predicting method.
Accepting the limits of suicide prediction

The best prospects for global suicide prevention do not involve traditional notions of suicide prediction or risk assessment. Reducing the suicide rate in countries with a high suicide rate or reducing the suicide rate of men to nearer that of women would achieve large reductions in global suicide rates. Attention to the care of hospitalized patients cannot be ignored because of the extraordinary suicide rate in this group, but this can only be expected to have a modest effect on total suicide rates because most suicides are by people who have never been in a psychiatric hospital. More generally, psychiatric treatment should be offered to all people in order to alleviate their burden of symptoms and should not be rationed or justified by notions of who is likely or unlikely to suicide. While some patients will generate more concern about suicide than others, knowledge of the limited sensitivity, modest power of discrimination, and the very low positive predictive value of suicide risk assessment should assist clinicians in the task of joint decision making with their suicidal patients.

Refraining from the temptation to predict suicide in clinical psychiatric practice might even assist suicide prevention. Low positive predictive values mean that most people who receive treatment because of a higher-risk categorization will never die by suicide and the limited sensitivity means that as almost half of the patients who do die by suicide might have been deprived of preventative measures after a lower-risk categorization. Epistemic judgements about future suicide should be made very carefully and only after all the available evidence is gathered. Valid statistical risk factors might contribute to such an epistemic call about suicidality, but this contribution should be modest.

Rather than attempt to make a suicide prediction, clinicians should focus on improving the interaction with the patient so as to foster hope, reduce the patient’s distress and suffering, and maximize the therapeutic alliance. A comprehensive assessment of the patient’s current needs should follow. These needs will often include the need to address modifiable factors that are associated with suicide, for example treatment of substance use, but most such needs should be met irrespective of the associations with future suicide. Needs assessments are not probabilistic and should lead to treatments being offered to all patients irrespective of perceived suicide risk.

Finally, psychiatrists should explicitly acknowledge the limits of prediction of suicide to our patients and their families and health care systems providers. Lowered faith in prediction and acceptance of the limits of prevention might have the benefit of reducing unnecessarily restrictive interventions and might allow clinicians to focus on more achievable treatment goals and the patient’s path to recovery.

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REFERENCES

20th anniversary issue

Alternative and complementary approaches in psychiatry: beliefs versus evidence

Pierre Schulz, MD; Vincent Hede, MD

Introduction

The power of human imagination has led our ancestors to consider the influence of celestial bodies, spirits, and gods on the horror of diseases and death. Over millennia, priests, shamans, sacred men, and medicine men helped their peers by predicting their fate and cure on the basis of various rituals, such as examining animal intestines or ingesting diverse compounds. The Jesuit Athanasius Kircher (1602-1680) wrote of interactions between planets, plants, and animals, and he considered God as the central magnet of all things. The physician Franz Mesmer (1734-1815) extended Kircher’s idea into application of the vital principle as a therapy for psychiatric symptoms for which there was then no therapy (Figure 1). In the United States, members of the Fox family declared by 1888 that their mediumnity was in fact a hoax, which did not stop the appeal of exchanging messages with the dead; only later in the 20th century did spiritism fall into some disrepute.

Frontiers between recognized treatments and charlatanism have long been a theme of discussion, and...
Louis of Jaucourt (1704-1779) wrote about this in the Diderot and d’Alembert Encyclopedia:

The desire to live is a passion so natural and so strong it is not surprising that those who in health have little or no faith in the skillfulness of an empiric with secrets, appeal nonetheless to this false physician in grave and serious illnesses, the same as those who are drowning cling to the smallest branch. They persuade themselves of having received aid, each time that skilled men did not have the effrontery to promise them a certainty.

Nowadays, complementary and alternative medicines (CAMs) are presented as safe, effective and affordable treatments, also for mental health problems. We discuss this category of approaches in mental care, excluding from this paper the role of traditional treatments in countries with little medical staff, where other traditional healers take care of the burden of disorders.

**Definition**

CAMs are diagnostic techniques and treatment practices outside mainstream and standard health care. It is said that complementary approaches are added to standard health care, while alternative ones are substitutes for it, a somewhat spurious non-operational nuance, because adding an alternative approach to a conventional one would make it complementary by definition. Integrative medicine is the combination of standard health care with CAMs, either simultaneously or successively. Some CAMs can be *a priori* labeled as charlatanism, ie, as useless approaches sold by charismatic healers to vulnerable customers.

We propose two qualifiers related to CAMs as well as to standard health care. We label as orthodox (from the Greek *ortho* meaning right or straight path and *doxa* meaning belief) those techniques that have adequately, ie, scientifically and rationally, been demonstrated to be efficacious and useful. The history of discoveries of orthodox methods starts with the first schools of medicine in the early Mediterranean world, even earlier elsewhere. We label heterodox those techniques that have been demonstrated as useless for diagnosis (iridology, astrology, etc) or as equivalent to placebo for treatment (homeopathy, prayer for others, etc) or for which there is no reason to hope for efficacy over that of placebo (protection through crystals, auriculo-therapy, aura therapy, Ho’oponopono, etc). Some heterodox approaches date back thousands of years. According to our proposed qualifiers, CAMs can be orthodox in given indications: biofeedback, neurofeedback, hypnosis, virtual reality techniques, mindfulness relaxation, omega 3 fatty acids, etc, while previously conventional approaches have been given up (frontal lobotomy, insulin coma, meprobamate), and many nowadays off-label prescriptions can be seen as heterodox.

**Clinical Illustration 1.** This 45 year-old patient is in ambulatory care because of severe depression. He had been doing clerical work for 15 years but lost this job because of conflicts with his boss. Psychotherapy, antidepressants, and augmentation treatment were without benefit. He consulted another medical doctor who ordered tests measuring neurotransmitters and their metabolites, amino acids, and immune globulins, and prescribed unusual treatment such as micronutrition and hormones. This gave the patient a feeling of being well taken care of, although his depression did not improve.

**Figure 1.** Franz Mesmer’s tub according to a 1784 French engraving

The tub (baquet) contained immersed bottles with magnetized water and iron fillings. Iron rods coming out of the tub were directed towards body parts and harmonica music was played while the patients held hands. Mesmer, who had fled from Vienna to Paris, was considered a genius by some and a charlatan by others. Eight members from the Académie de Médecine and the Académie des Sciences demonstrated that the tingling, trembling, tears, and even convulsions observed in persons who knew they were being magnetized were absent when subjects were magnetized while being unaware of it.
Practitioners of heterodox approaches have attempted to have their techniques accepted as orthodox, for example orgone machines by Wilhelm Reich, primal therapy by Arthur Janov, orthomolecular psychiatry by Carl Pfeiffer. Treatment of depression under hallucinogens, psychoanalysis, narco-analysis, and psychosurgery shifted from being heterodox to orthodox, only to be later considered again as heterodox or possibly so. Some approaches are difficult to label as either orthodox or heterodox because of lack of clinical studies or because of the unusual aspect of the method: pet-assisted therapy, visual and acoustic brain stimulation machines, fecal microbiote transplant in psychiatry, etc.

**Multiplicity of complementary and alternative medicines**

CAM techniques are many and can be classified as mainly biologically based (phytotherapy, diets, massage) or addressing the mind/body relations (relaxation, techniques of energies balancing, therapeutic action at a distance). Clients searching for relief from psychological suffering can use, to quote a partial alphabetical list of CAMS, acupressure, acupuncture, animal-based therapy, anthroposophy, atlas repositioning, astrology, aura therapy, auriculotherapy, Ayurveda, bracelets and medals, Coué method, cryogenic whole body therapy at minus 100°C, crystals and minerals, DNA healing over the phone, energy techniques based on auras or chakras, essential oils, family constellation therapy, homeopathy, massages, osteopathy, pendulum dowsing, reiki, relaxation, regression towards previous lives, sensory deprivation, special shoe soles, talking to angels, touch therapy, urotherapy, etc. Within a given CAM category, one can obtain diverse effects: *Saint Gabriel* incense helps with making the right decisions, while *Padre Pio* incense decreases stress and anxiety. CAMs can be associated, for example in phyto-astrology or litho-chakra-numerology.

**Reasons for choosing CAMs**

Reasons put forward by persons who choose CAMs are many: natural treatments are better than chemical ones, psychotropic medications are not systematically effective and induce side effects, pharmaceutical industries aim only at their own profit, physicians consider functional symptoms as not being diseases, physicians do not spend enough time with patients, conventional treatment is not well reimbursed, wellness is a higher goal than the mere decrease in symptoms, viewing a person as a whole leads to a more human society, modern science bridges with ancient wisdom, the normal state of Mother Nature is health, CAMs and other heterodox approaches generate hope. People are induced into using CAMs by the fact that science education is neglected, by the existence of national and international conferences on CAMs, and by the lack of state regulations and recommendations.

Suggestion is another reason for choosing CAMs. It leads to reassurance and empowerment of the client: the therapy will work because the CAM practitioner says so, and because he or she indicates that it restores harmony and balance within bodily and mental energies. This is often felt as psychologically more comfortable than a medicine driven by technology, even if centered on the patient, with its probabilistic predictions based on the complexity of clinical status, familial medical history and paraclinical testing (epigenome, metabolome, proteome, genome, etc) and, in psychiatry, neuropsychological testing and neuroimaging. Even this knowledge does not suffice to build certainty and uncertainty remains an arduous concept for patients and doctors to acknowledge. With CAMs, empowerment arises from the ease of understanding simple causes and mechanisms that are not mingled: energy channels (acupuncture), toxic substances (detoxification), energy transfer (subtle bodies therapy), the same cures the same (homeopathy), the state of internal organs is projected on the ear, the feet, or the iris (auriculotherapy, foot massage, iridology), the precise choice of the therapeutic substance (bioresonnance), etc. Some CAMs are said to be efficacious for many, if not almost all, ailments, and this totalizing approach is also reassuring.

**Clinical illustration 2.** *This young man has just been diagnosed with bipolar II disorder. His psychiatrist did not propose a clear cause for the onset of the disorder. A naturopath firmly explained the link between the symptoms and a family loss in the patient’s early childhood. He offered a treatment based on herbs, in order to balance vital energy.*

Confirming the opinion of the majority is yet another reason to choose CAMs: one reads that homeopathy is not superior to placebo, but people hear friends...
tell their success story of having benefited from it. Also, some medical doctors become practitioners of CAMs.

**Clinical illustration 3.** This 45-year-old woman works as a surgeon in emergency and other hospital services. Because she felt a lack of human relations with her patients, she decided to compensate for this by acquiring competence in the fields of acupuncture and homeopathy, two CAMs that she then offered to hospitalized patients.

Personality, but also culture and education play a role in the tendency towards belief in the paranormal: immigrants from Africa to Europe might combine witchcraft and modern medicine knowledge to explain their symptoms. All these reasons explain that anxious or depressed persons more often use CAMs than orthodox treatments, and this has a high financial cost.

**Mechanisms of action**

Several mechanisms of action are non-specific and common to all CAMs. The first one is suggestion, asserted by the success of the French pharmacist Coué’s method of conscious autosuggestion exemplified by his sentence “every day, in every way, I am getting better and better,” by the number of self-help books, by the benefits of placebo, and by the idea that doctors, professors, or gurus (in the orthodox and heterodox domains respectively) are powerful therapists. A second common mechanism of action is giving the patient enough time to feel listened to and understood as an individual. A third mechanism common to several CAMs is the induction of a restful state during the sessions.

There are potentially specific mechanisms of action for some CAMs. The pharmacological effects and modes of action of phytotherapy extracts or purified substances have been recently studied using the same technologies as for pharmaceutical products discovery: high-throughput screening, biomarkers identification and system biology approach. Animal models of behavioral and biochemical changes have also been used for the study of CAMs’ mechanisms of action. As laboratory studies or animal studies are easier or less costly than clinical trials, there is an abundance of such protocols on CAMs, for example the effect of acupuncture on neuropeptide Y in the basolateral amygdala of maternally separated rats, or its influence on brain networks activation in humans. In summary, there are many fundamental laboratory and too few clinical studies of CAMs, a regrettable situation, somewhat akin to that with conventional therapies. These fundamental studies have, however, not yet established well-defined specific mechanisms by which a given CAM might act.

**Efficacy**

Most CAMs have not been studied with placebo-controlled trials and selected randomized patients. When such studies were done, the results were often equal to placebos. Also, results about a given CAM were more positive in countries where it was already widely used. There are no studies on the associated administration of CAMs, and few studies on the addition of CAMs to orthodox treatments. Some studies show astonishing results: while trials of praying for another person generally showed no health effect or were criticized for their methodology, there is one study where North Americans who prayed for 199 Korean women undergoing in vitro insemination doubled the fecundation rate, from 26% to 50% of success. Sectarian religious groups are particularly prone to the diffusion of miracle cures, and televangelists shout: “Depression, in the name of Jesus, go away… go away… demons go away.” The fact that a CAM dates back hundreds of years is quoted as an argument in favor of efficacy. Should black bile theory still be accepted, just because Hippocrates described it? Or bloodletting, outside of cases of hemochromatosis? Simple protocols can test hypotheses underlying given CAMs, for example by testing whether therapeutic touch practitioners are capable of identifying whether or not there is a person behind a thin opaque screen.

CAMs’ efficacy is often alluded to on the basis of single cases. On the internet and/or other media, one has access to many stories where a CAM practitioner has interrupted years of a patient’s suffering from bipolar disorder, depression, or schizophrenia just with a naturopathic treatment like homeopathy. These are indications either that the CAM prescribed was efficacious for that person in that situation, or that the syndrome improved spontaneously. Some CAMs are considered efficacious in the absence of controlled clinical trials: yoga, adequate diet, physical exercise might help in cases of depression. Thus, adding these CAMs to a conventional treatment might be useful. This does not apply to other CAMs such as micronutrition, homeopathy, or...
bioresonance. Despite the lack of evidence for efficacy of many CAMs, a Beijing Declaration was adopted in 2008 to call on WHO Member States and other stakeholders to “take steps in order to integrate traditional medicine and CAMs into national health systems.” This would, at least in part, represent accepting the use of impure placebos, ie, placebo not limited to a pharmaceutically inert substance.

Finally, outside of the realm of CAMs, many non-medical interventions are very beneficial, such as prevention of addictions, school bullying, child maltreatment, and others; studies on these primary prevention interventions are of paramount relevance to mental health.

**Side effects**

Many CAMs imply a form of magic world, with immediate diagnoses, powerful transfers of energy, a chemically purified body, etc. These ideas go as far as believing that entities from advanced planets take care of us, or that gurus survive without food by just being exposed to light. Thus, a first side effect of most CAMs is a facilitation of paranormal beliefs, an alienation from rational thinking. This side effect is of little medical or psychiatric consequence for healthy people, but it can deter fragile or sick persons from the necessary orthodox diagnostic and treatment approaches.

**Clinical illustration 4.** This woman was dying from pancreatic cancer and she only received homeopathic medicine from her medical doctor until her son asked another doctor to prescribe opioids.

The dark side of suggestion is the nocebo effect, potent to the point of leading to voodoo deaths. Opposing innocuous CAMs to the danger of orthodox medications and treatment increases the nocebo effect of these approaches.

**Clinical illustration 5.** This 50-year-old man refused to take an anxiolytic and inquiry into the reasons for his refusal led to the discovery of his profound dislike of chemical medicine and to the fact that he had been non-compliant with the oral oncologic medication for weeks.

The goal of achieving harmony between mind and body, between flows of energy, common to several CAMs, can present itself in non-realistic terms.

**Clinical illustration 6.** A 16-year-old boy was treated for a delusional disorder, including the belief in his psychokinesis. His parents rejected medical help for weeks, because their own kinesiologist had assured them that a few persons are indeed endowed with the ability of psychokinesis, of moving objects around without touching them.

The cost of treatment becomes a side effect when inefficacious CAMs are expensive. There are also side effects specific to given CAM. Acupuncture can lead to hematoma pneumothorax, chylothorax, and perforation of abdominal organs. Psychotic breakdowns or dissociative states can occur after dialogues with the dead, travel towards former lives, hypnosis, deep relaxation through meditation and massages. Yoga can lead to physical trauma. CAMs practitioners often have insufficient training about efficacy and side effects.

**Clinical illustration 7.** The mood swings of this 40-year-old man with bipolar I disorder were stabilized with psychotropic drugs. Despite good professional training, he had been unemployed for several years. In order to get a job, he asked a coach for assistance. The latter convinced him of the uselessness of drugs, telling him that he should only rely on himself. The patient kept seeing the coach until his hospitalization for severe mania.

**Clinical illustration 8.** This 30-year-old European woman travels to India for an Ayurvedic treatment. A severe acne breakout develops while there: she is told that this is the sign of toxin removal. Back in Europe, she is proposed isotretinoin by a dermatologist, not a wise prescription because of her medical history of severe delusional depression.

CAMs practitioners, aside from the caricatural behaviors illustrated in several of the above clinical illustrations, also give wise advice such as getting enough exercise, avoiding unhealthy food, taking time to meditate; this has few side effects, aside from some people becoming obsessed by their cautious life habits.

**Sources and quality of information**

There exist few valuable sources of information outside of state-funded institutions such as the National Center for Complementary and Integrative Health (NC-
CIH) in the United States, the National Health Service (NHS) and the National Institute for Health and Care Excellence (NICE) in Great Britain. Through the NC-CHI readers have free internet access to the CAMs they are interested in, the syndrome they wish to know about, and how to treat it if they choose CAMs. The information is presented in a manner that assumes that the reader is capable of understanding clinical trials, meta-analyses, and evidence-based medicine (EBM). Collaborators of the Canadian CANMAT have made recommendations as to the use of CAMs in cases of depression. The French Academy of Medicine recognizes acupuncture, osteopathy, tai-chi, and hypnosis as being of possible value in given medical backgrounds, and homeopathy of absolutely no value. The Skeptic’s Dictionary, available through the Internet, offers an extended list of critical analyses of CAMs that can help readers in their choices. The 2012 Flying Publisher Guide to Complementary and Alternative Medicine Treatments in Psychiatry is of high quality and freely accessible on the Internet, as are the many comments from the Society for Science-Based Medicine pertaining to CAMs regulations in the United States.

The Cochrane Collaboration reviews and the clinical trials of CAMs mentioned in PubMed are a valuable source of information. Their content gives indications where CAMs could be useful, but mostly illustrates the need for more studies, with the frequent occurrence of series of words such as “may be effective,” “larger more powered trials are needed,” “methodological flaws limiting definite conclusions,” “positive findings are reported... but there is currently insufficient research evidence for firm conclusions to be drawn,” etc.

Not all sources of information are of quality, even when of official nature. For example, the Internet portal Evidence Based Acupuncture mentions the 2003 World Health Organization Report on Acupuncture, with the 28 syndromes and disorders for which acupuncture was considered proven through controlled trials to be an effective treatment, including renal colic or malposition of the fetus. Except depression, there was no psychiatric syndrome in this first list, but in the next list of 63 conditions where “therapeutic effect has been shown but for which further proof is needed,” one finds alcohol, cocaine, heroin, opium and tobacco dependence or detoxification, fibromyalgia, male sexual dysfunction, premenstrual syndrome, schizophrenia, Tourette syndrome, and vascular dementia. The conclusions from the above review seem quite optimistic, despite the term “evidence-based” being in its title.

Many journals for the general public participate in the diffusion of favorable opinions about CAMs. In order to adapt their message in a science-oriented culture, their journalists publish side-by-side articles dealing with real science (such as precise descriptions of neuroimaging results in psychiatric disorders) and articles on angels having saved a child’s life. This mix of truthful and bizarre information blurs the distinction between peer-reviewed information guaranteed by a self-corrective social system, and irrational belief in paranormal events, to which a proportion of CAMs refer. One finds misleading statements in the media that “the reality of mediums’ interventions and powers are now proven by research in university centers” or that “human consciousness is explained by quantum physics.” The French astronomer Camille Flammarion (1842-1925) is a historical example of a man of science having had irrational ideas: he asserted that the discovery of radio and telephone would lead to confirming telepathy. A few well-known contemporary scientists are fond of unproven ideas and they publish books, host television shows, and have internet portals. The Internet offers information of dubious quality concerning both heterodox and orthodox approaches, and this is the price for the otherwise justified concept of information transparency.

Clinical illustration 9. This 60-year-old man with a university education and training spends hours searching the Internet about treatments for his mood disorder, and participates in discussion on the Internet. He confronts his psychiatrist with all this information and asks him to comment in detail on other medications and why he should or should not try them. He thinks that psychiatrists work mainly for pharmaceutical companies, and that there exist potentially useful but unknown compounds outside mainstream prescriptions.

There are institutions dedicated to the control of false and misleading advertisement, such as the Federal Trade Commission in the United States. In France, the French Trade Commission in the United States. In France, the French Academy of Medicine who became critical of CAMs.
All sources of information, and those on CAMs are no exception, confront readers with the uneasy task of evaluating the veracity of what is described. CAMs practitioners assume that patients are able to decide for themselves. (This applies also to orthodox approaches and to the promise of revolutionized medicine thanks to microtechniques and artificial intelligence).17 Once a belief is established, the discovery of facts contradicting it (ie, knowledge rather than conviction) does not automatically lead to a new belief. This is true of declarations about the inefficacy of CAMs such as homeopathy, as well as of acceptance of scientific discoveries.18

**Conclusion**

Decades ago, lots of people considered CAMs as quackery or fraud. This has now changed and the present diffusion of CAMs, with hundreds of methods and thousands of practitioners in occidental countries, is neither a sufficient nor a satisfactory argument to accept CAMs as a regular approach in treating psychiatric syndromes, despite the empathy and the good intentions of many CAMs practitioners to alleviate human suffering.

There are four major explanations why CAMs are more largely used than justified by the controversies about their clinical efficacy. First, appreciation of occult sciences and magical ideas isn’t limited to the dark ages of sorcery: it also represents an appealing option in times when society is felt to be dominated by science and reason, and paralogical thinking might presently be among the substitutes for the decrease in traditional religiosity. Second, practicing CAMs is a developing means of financial gains. The Internet has facilitated these gains by offering greater access to consumers, and CAMs consultations by telephone are billed or offered after receipt of a check. Third, some members of the medical profession, even within university hospitals, endorse CAMs. Patients in given oncology units systematically receive hypnosis to decrease their anxiety and depression, or the phone number of the person who will “make the secret,” ie, say special incantations that will prevent side effects of oncologic treatments. In fact, patients prefer hospitals where CAMs are also offered.19 A fourth reason for the diffusion of CAMs is the limitation of efficacy in heterodox approaches in psychiatry and other specialties.

Our recommendation to distinguish orthodox from heterodox approaches in health care offers an operational criterium for a classification that enables placing each CAM along a continuum from clearly heterodox to clearly orthodox, ie, an incentive towards a wider use of the methodology of EBM for the evaluation of CAMS. Most of the work in view of the orthodox/heterodox CAMs classification remains to be done, because of the lack of relevant previous clinical research studies,20 the methodological issues with these studies, and the lack of registration requirements and practice regulations for CAMs. It is necessary to identify CAMs for which there is compelling evidence of their uselessness, to disseminate these facts, and to inform the public in what cases they are paying for a method akin to a placebo. With CAMs that might be somewhat superior to placebo, studies should address the questions of numbers and frequency of sessions, role of the experience of the therapist, relative efficacy towards conventional approaches, and consequences of associating CAMs with conventional treatments.

The task and challenge within the coming decade should be to draw frontiers between acceptable CAMs and charlatanism, ie, to clearly differentiate truly inefficacious CAMs from the few that have, or might have, useful therapeutic or preventive effects at least slightly above placebo effects. Moreover, studies should be set up to evaluate the best modalities for the transfer of objective information about CAMs, to explore how patients understand EBM when their medical doctor prescribes homeopathy, when the insurance reimburses this prescription, and when CAMs practitioners describe their treatments within simplistic overarching mechanisms.

On the condition that these different categories of studies could be carried out, better state regulations as to CAMs teaching, certification, and practice might be set up. In short, the requirements of EBM should be applied to CAMs’ evaluation. All this will be arduous, because of financial interests linked to CAMs and because of the not too fashionable, to say the least, promotion of reasonable doubt in the search for veracity. ❐

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The debate regarding maintenance treatment with antipsychotic drugs in schizophrenia
Michael Davidson, MD

Introduction

Serendipitous observations and research conducted between the 1950s and the 1970s provided uncontroversial evidence that drugs which block dopamine (DA) receptors ameliorate acute agitation, delusion, hallucination, and thought disorder, all characteristics of the schizophrenic illness. Because the natural course of schizophrenia is characterized by alternating periods of psychotic symptom emergence, improvement, and re-emergence, researchers in the 1970s and 1980s investigated the possibility that the same DA-blocking drugs might also reduce the risk of symptom re-emergence.

Several large meta-analyses of maintenance trials have confirmed that patients who suffer from chronic schizophrenia, randomized to placebo, are likely to experience earlier symptomatic worsening than patients randomized to a dopamine (DA)-blocking drug. These findings led expert groups to issue treatment guidelines, which recommend treatment with DA-blocking drugs for periods ranging from several years to indefinitely. The recommendations were accepted by the majority of, but not all, the experts, some of whom proposed a targeted or intermittent therapy approach by which DA-blocking drugs are discontinued upon symptomatic remission, to be renewed in case of symptom re-emergence. The debate between continued and targeted treatment approaches arises from disagreements regarding scientific and ethical questions. Scientifically, the discussion focuses on the quality and interpretation of the supporting or detracting evidence regarding each treatment option. For example, what is the percentage of individuals who can maintain stability off drugs? What is the rate of individuals who exacerbate despite maintenance treatment? What is the percentage of individuals who experience drug-related adverse effects? How can we interpret results of open-label, nonrandomized targeted trials? Regarding ethical questions, the debating sides disagree on how to weigh the impact of the decreased risk for exacerbation versus the certainty of adverse effects on the patient’s quality of life, and how to reach a patient-therapist shared decision within the constraints of mental illness.
The fact that the same drug might ameliorate symptoms during a disease flare-up can also reduce the risk of future flare-ups is well-documented in medicine: for instance, steroids ameliorate flare-ups and of rheumatoid arthritis and reduce the risk of future flare-ups.3

A comprehensive meta-analysis of placebo-controlled maintenance trials has confirmed that patients randomized to placebo are likely to experience earlier symptomatic worsening compared to patients randomized to a DA-blocking drug.4 These findings have led professional organizations and expert groups to issue treatment guidelines recommending that individuals who manifest acute psychosis and meet diagnostic criteria for schizophrenia should be treated with DA blocking drugs for 1 to 3 years after symptom reduction or remission.5 Despite some variability between guidelines, it is also recommended that individuals who experience symptom recurrence should continue treatment for many years to indefinitely.6-8 The recommendations regarding the treatment of the acute phase of the schizophrenic illness are almost beyond debate. However, those regarding continuous maintenance treatment have been adopted by most researchers and clinicians10 but questioned by others.11-15 The latter proposes a targeted therapy approach by which DA-blocking drugs are discontinued upon symptomatic remission and renewed only in case of symptoms re-emergence.

Despite some reservations,16 the case for continuous maintenance treatment is straightforward in that the risk for symptoms re-emergence persists long after resolutions of the acute symptoms. The argument recurring in several comprehensive reviews9,10,17 is that the short- and long-term impact of exacerbations and hospitalizations on the patients’ well-being justifies the immediate and cumulative adverse effects of the drugs. Since there are no diagnostic markers that distinguish between individuals who can maintain very long periods of symptom stability or remission in the absence of DA blocking drugs and those who would experience exacerbation,18 and since the impact of exacerbation is harmful and demoralizing, all individuals affected by chronic schizophrenia should be encouraged to accept continuous, long-term maintenance treatment.

The case for the targeted treatment approach argues that, like almost all medical interventions, maintenance treatment has immediate and accumulating adverse effects; therefore, its use should be restricted to the minimum regarding dose and duration. Specifically, acutely ill patients should be treated until stabilized, after which the dose of medication should be reduced and subsequently discontinued. Should acute symptoms re-emerge, the same cycle and procedure are to be repeated. Several follow-up studies supporting this approach have indicated that schizophrenic patients on a targeted treatment have better long-term outcomes, in terms of social and vocational performance than those on continuous treatment.19-27

The debate between continued and targeted treatment approaches arises from disagreements regarding scientific and ethical questions.28 Scientifically, the debate focuses on the quality and interpretation of the supporting and detracting evidence regarding each treatment option. For example, what is the percentage of individuals who can maintain stability off drugs? What is the percentage of individuals who exacerbate despite maintenance treatment? What is the percentage of individuals who experience different drug-related adverse effects? What is the clinical significance if any, of brain volume loss? How to interpret results of targeted trials, most of which are open-label, non-randomized trials? On the ethical aspect, the debating sides disagree on how to weight the impact of the decreased risk for exacerbation versus the certainty of mild-to-moderate AE and the risk of severe AE on the patient’s quality of life.29

Critique and defence of the continuous maintenance approach

Dopamine sensitization

Continued blockade of DA receptors may cause receptor super-sensitivity, which might, upon abrupt discontinuation of antipsychotics, contribute to rapid and frequent exacerbation.11,30 This idea is supported by studies in rodents demonstrating that chronic treatment with antipsychotics increases DA receptor densities.31 It is argued, the worsening of symptoms upon discontinuation of antipsychotics might reflect the effect of withdrawal rather than loss of the benefit of the drugs.32 An alternative explanation for rapid worsening upon drug discontinuation is the possibility that antipsychotic drugs with intrinsic anticholinergic effects produce cholinergic rebound upon discontinuation, which manifests as general malaise and can be mistaken for symptom worsening.33 However, a meta-analysis that looked at trials comparing
abrupt versus gradual discontinuation of DA-blocking drugs found no differences between the two modalities regarding symptom worsening. Recent publication supports this assertion, showing that most relapses occur months and years after discontinuation rather than upon or immediately after discontinuation.

**Brain volume loss**

Meta-analyses of imaging studies have demonstrated a correlation between cumulative exposure to antipsychotics and gray-matter loss, which in turn might be responsible for the cognitive and social impairments observed in schizophrenia. Still, loss of brain tissue has been reported in premorbid and first-episode patients who were drug-naïve or had received antipsychotics only for brief periods of time. An alternative explanation posits that larger cumulative doses of antipsychotics could reflect a more severe form of illness, which could be associated with tissue loss. However, at least one study indicates that the correlation between cumulative exposure to antipsychotics and tissue loss is maintained even when controlling for severity of illness.

**Premature death, metabolic abnormalities, and cardiovascular morbidity**

It is well-established that schizophrenic patients die earlier than age-matched controls, and that antipsychotics drugs increase risk for diabetes, abnormal blood lipids, and weight gain, which in turn increase risk for cardiovascular disease and death. However, other reasons, such as poor access to medical care and suicide, might contribute to premature death. Furthermore, data indicate that compliance with antipsychotic medication might reduce death rate. One explanation for such discrepant findings is that the reduced rate of death associated with compliance to antipsychotic treatment reflects a general tendency to be compliant with medical treatment and a healthier life style, rather than a direct benefit of antipsychotic drugs.

**Lack of ecological validity and other methodological limitations**

Most maintenance placebo-controlled trials last between 6 and 12 months, which might be too short for an illness with a lifetime course to be informative. Also, events such as violent outbursts or even hospitalizations, used as outcomes in maintenance trials, are not necessarily surrogates for illness worsening and exacerbation but could reflect the reaction of society to any aberrant behavior in an individual with a diagnosis of schizophrenia. Furthermore, maintenance trials comparing a DA-blocking agent with placebo cannot be truly blinded since the drugs have AE that are known and anticipated by both patient and the investigator/rater, which biases the results in favor of the active drug over placebo.

**Poor tolerability affecting patient’s quality of life**

Antipsychotics differ regarding tolerability profile, and individual patients experience each adverse effect differently, but none is devoid of tolerability problems. Akathisia, stiffness, tremor, apathy, sedation, lethargy, avolition, slowness of movement, and weight gain are AE which affect a patient’s daily life. Furthermore, since some of the AE are visible to others, it might amplify the stigma associated with the illness. Using the minimal effective dose and supplementing with anticholinergic drugs might mitigate a few but not most of the AE.

**Limited effectiveness**

DA-blocking drugs, initially known as major tranquilizers, are effective mainly for acute agitated behavior and some aspects of psychosis, while the phenomenology of schizophrenia includes negative symptoms, impairment in judgment, and cognitive and social functioning, impairments on which the DA-blocking drugs have no direct therapeutic effect. On the contrary, they may even produce secondary negative symptoms in addition to the intrinsic primary negative symptoms. Indeed, patients followed for a very long time off antipsychotics have less negative symptoms compared to treated patients. Since DA neurotransmission mediates brain reward circuits, it can be hypothesized that blocking DA receptors might deprive patients of experiences of pleasure and expecting reward(s).

Furthermore, questions have been raised as to whether improvements on psychometric scales, while being sufficient to demonstrate statistically signifi-
Significant differences between drug and placebo, are also clinically meaningful.\textsuperscript{56-59} Even if the advantages are clinically meaningful, it is not obvious whether maintenance treatment has a real impact on the social and vocational reintegration of patients, most of who remain socially isolated and unemployed.\textsuperscript{60} Moreover, the beneficial effects of antipsychotics seem to decrease as a function of study duration.\textsuperscript{4} Proponents of the continuous treatment hypothesized that the biological effect of the drugs remains unchanged, but as the trial continues, compliance with treatment decreases, nullifying the advantage of being in the active arm versus the placebo.\textsuperscript{10}

It is also accepted that several biologically distinct abnormalities probably coexist under the diagnostic umbrella of schizophrenia,\textsuperscript{61-63} making it improbable that the same pharmacological intervention—interference with the DA neurotransmission—would be effective for all subgroups. In maintenance trials at least 20\% of the patients randomized to the active drug have the same time course in terms of symptoms as those randomized to placebo,\textsuperscript{4} and antipsychotics appear to lose efficacy after 5 to 10 years of treatment in about two-thirds of the treated patients.\textsuperscript{64} Between patients who can maintain remission without need for antipsychotics and patients who are actively psychotic despite antipsychotic treatment or treatment-resistant,\textsuperscript{63} it seems that a considerable number of patients are subjected to the adverse effects of antipsychotics without clear benefit.

### Critique and defense of the targeted treatment approach

#### Risk of exacerbation

Trials comparing early versus late discontinuation of antipsychotic drugs in first-episode patients demonstrated higher exacerbation and hospitalization rate in the former group.\textsuperscript{34,65} Controlled trials comparing targeted versus continued maintenance treatment in chronically ill patients reported more exacerbation and hospitalization in the targeted arm.\textsuperscript{66} Furthermore, relapses may impact the long-term outcome negatively as symptoms may not return to pre-discontinuation baseline.\textsuperscript{67} However, contrary evidence also exists, indicating that when antipsychotics are reinstated, symptoms return to baseline.\textsuperscript{58,64}

#### Selection bias and reverse causality

Trials that demonstrated better outcome(s) after several decades of follow-up of patients receiving targeted or no maintenance treatment at all did not use a random assignment design\textsuperscript{70} or utilized old, inadequate methodologies,\textsuperscript{71} and the results were affected by attrition bias.\textsuperscript{72} Patients with less severe symptoms at baseline might have been selected for follow-up when off drugs, while patients with a more severe illness at baseline were followed up when on drugs.\textsuperscript{73,74} However, even if that has been the case, it still demonstrates that a subgroup of above 20\% of patients with a diagnosis of schizophrenia does not experience psychotic symptoms in the absence of antipsychotic drugs.\textsuperscript{65} Furthermore, at least one study demonstrating the advantages of targeted therapy used a random assignment design.\textsuperscript{76}

### The ethical dilemma

Having seen repeated exacerbations, patients’ anguish, hospitalization, and socially unacceptable behaviors of patients who discontinue medications, most psychiatrists and mental health workers concur with the guidelines and advise patients and their families to adhere to continuous maintenance treatment.\textsuperscript{77} However, a very high percentage of patients discontinue medications against medical advice.\textsuperscript{78} Others titrate their own medications to avoid AE, or take medications only when they believe their symptoms are getting worse. Some patients insist that medication discontinuation be attempted, despite concurring with medical advice. Since impaired judgment characterizes schizophrenia, the patients’ negative attitude towards medication might be attributed to poor insight into the illness and the benefits of medication.\textsuperscript{79,80} This view, although not devoid of scientific support,\textsuperscript{81} aligns poorly with notions of respect for patients’ autonomy\textsuperscript{82,83} and shared decision-making.\textsuperscript{84,85} To complicate matters even more, it is also conceivable that some patients who do not adhere to their prescribed treatment are making informed decisions that the increased risk of symptom worsening is preferable to the certainty of adverse effects.\textsuperscript{86} Such decisions are supported by the existence of subgroups of patients who would maintain symptom stability and would better function socially and vocationally when off antipsychotic drugs.\textsuperscript{87} Regardless of the final decision if to stay on medication or not, physi-
Ciancians have the duty to protect patients from making bad treatment decisions.88

Although results of well-conducted trials are the foundation of clinical decision making, physicians’ psychological biases might also play a role. The recent memory of the last patient who has discontinued treatment, exacerbated, and “got into trouble” (ie, availability bias) 89 probably affects treatment decisions more than the patients who were lost to follow-up and were doing well without any treatment.90 Likewise, negative outcomes, such as risk for exacerbation, hospitalization, or aberrant behavior are given more weight in medical decisions than positive outcome, such as the certainty of living without the AE of drugs (ie, negativity bias).91

While the main priority for a treating psychiatrist is to avoid symptom exacerbation and hospitalization, for a patient it might be looking slim and avoiding stiffness.11

### Conclusion

In summary, despite the benefits of DA-blocking drugs for some aspects of schizophrenia, available data have not provided satisfactory answers to the dilemma raised by maintenance treatment,92 for the practising clinician who treats patients with residual and/or negative symptoms or who are reluctant to accept the adverse effects of DA blocking drugs (see World Psychiatry Forum 2018). Future research will have to address these questions: (a) what should be the criteria for the selection of candidates for discontinuation of maintenance treatment? (b) how can we ascertain that the patient indeed understands the risk and benefits of treatment discontinuation? (c) once discontinued, how can we distinguish, in a “vulnerable” individual, between normal reaction to daily life stresses and impending symptom exacerbation requiring re-instatement of treatment, or what should be the threshold for reinstating treatment? (d) are any of the suggested protective factors such as abrupt onset, female gender,93 or biological markers94 clinically useful? (e) and, is past experience of early95 and protracted stability, or of rapid exacerbation, predictive of the same in the future?93

Hopefully, current research will produce better-tolerated drugs for schizophrenia, targeting negative symptoms96 and cognitive impairment, which do not necessarily block DA receptors97,98 hence, devoid of the associated adverse effects.

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Should antidepressants be used in minor depression?

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Minor depression is not a minor disease

Most patients, suffering from depressive symptoms, do not reach minimum diagnostic criteria (number, severity, or duration of symptoms are insufficient) of major depression and are diagnosed as having minor or subsyndromal or subthreshold depression. For subthreshold depression, different definitions exist, based on the number of depressive symptoms, duration of symptoms, exclusion criteria, and associated functional impairments. Judd et al defined subsyndromal somatic depression as “any two or more simultaneous symptoms of depression, present for most or all of the time, at least two weeks in duration, associated with evidence of social dysfunction, occurring in individuals who do not meet criteria for diagnosis of major depression and/or dysthymia.”

The major public health relevance of minor/subthreshold depression has been underlined by numerous studies, but reported rates vary dependent on the definition. Minor/subthreshold depression is associated with functional impairment, reduced quality of life, and the risk of developing into major depression. Therefore, it should be treated. Watchful waiting should be an option only for patients who, despite adequate information, are not interested in any kind of treatment. Psychotherapy has been found to be effective, but due to methodological problems (control group, blinding), efficacy derived from randomized trials might be overestimated. Studies on the efficacy of antidepressants in the treatment of minor depression have found clinically relevant benefits over placebo, particularly the newer, better-controlled trials. One major advantage of antidepressants over psychotherapy is their immediate availability and the short period required to evaluate efficacy. Aside from the severity of depression, the patient’s attitude towards psychotherapy or antidepressant treatment is of major relevance and should be explored. In a shared decision-making process, the patient should receive appropriate information on treatment options, state her or his preferences, and then receive the treatment of choice.

Keywords: antidepressant; minor depression; psychotherapy; subthreshold depression

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tions used: 2.5% to 9.9% in community samples or 5% to 16% in primary care patients with higher prevalence particularly in elderly patients. In each of these settings, there are two to three times as many persons with depressive symptoms that fall short of fulfilling all criteria of major depression.

The term “minor depression” is misleading, as this “minor” disease is associated with marked psychological suffering, significant decrements in health, problems with activities of daily living, and a marked reduction in quality of life. Moreover, minor depression is also a strong risk factor for major depression. One study found that major depression develops in 10% to 25% of patients with subthreshold depression within 1 to 3 years. Minor depression/subthreshold depression is also associated with increased service utilization, suicidality, and mortality. These findings suggest that although minor depression is milder than severe depression, it is not a mild or minor disorder, and it should be recognized, diagnosed, and treated early.

Early and effective treatment is needed

The benefit of adequate treatment has been shown in many studies, particularly regarding long-term outcomes. However, there is some disagreement about the effectiveness of different treatment strategies, which include watchful waiting, herbal medicine (eg, St John’s wort), psychotherapy, or psychopharmacological treatment with antidepressants.

Watchful waiting means no treatment and is associated with the dubious expectation of fast improvement and good prognosis. Watchful waiting, although suggested in some guidelines, might not be a sufficient treatment because of the risk of transition from minor to major depression, functional impairment, and the reduction of quality of life, which is observed already in minor or subthreshold depression. Candidates for watchful waiting may be only patients with good social support, lacking a family history of depression and refusing psychological or pharmacological treatment despite full information about the risks of the disease and available treatment options.

Herbal medicine, mostly St John’s wort medication, is particularly popular among patients, who do not like to take “chemicals” but prefer “natural treatment.” However, the efficacy of herbal medicine is controversial, as most trials have not found benefits over placebo in patients with major or minor depression.

Efficacy of psychotherapy

The efficacy of psychological treatment of minor/subthreshold depression has been examined in a meta-analysis of randomized controlled studies. Seven studies with 700 subjects were included and the mean effect size was 0.41 with very low heterogeneity. The relative risk of developing a major depressive disorder in subjects who received the psychotherapeutic intervention was 0.70. The authors conclude that psychological treatments have significant and beneficial effects on subthreshold depression and that these interventions may prevent the onset of major depression.

Divergent findings have been reported for the effectiveness of psychotherapy in the treatment of depressed patients in primary care practice. Twelve studies on the treatment of patients suffering from major depression, minor depression, or dysthymia were analyzed. Since earlier studies were methodologically flawed, Schulberg et al considered only studies which employed not only efficacy, but also effectiveness designs, used standard diagnostic assessment procedures, appropriate follow-up periods, empirically evaluated treatment manuals, and adequate comparison conditions. The authors’ conclusion is that in the treatment of major depression, a depression-specific psychotherapy produces outcomes which are similar to those produced by pharmaceutical therapy, but better than primary care physician’s usual care. Thus, regarding psychotherapy in the treatment of minor depression, the evidence is equivocal and further studies are needed to determine whether psychotherapy should be recommended as a first-line intervention.

Studies on efficacy of psychotherapy and the resulting effect size have to deal with the fundamental and unresolved problem that neither the patients nor the therapists can be blinded concerning the treatment condition. Without the possibility of blinding, patients who know to be in a control, eg, “only a waiting list” group will not profit from a placebo effect, but might often be frustrated. Therefore, randomization into the control group could even result in a negative (nocebo) effect. This hypothesis is supported by a study investigating the efficacy of sertraline, placebo, cognitive-behavioral therapy, and moderated self-help group in primary care patients. The outcome in the moderated self-help group (serving as psychotherapy control group) was significantly worse than in the drug placebo group, as well as in all other groups. Due to the diffi-
Faculty of providing an adequate psychotherapy placebo, studies on the efficacy of psychotherapy might result in overestimated treatment effects. Several studies have addressed and thoroughly analyzed factors leading to an overestimation of effects of psychotherapy in clinical studies on depression.27,28

Efficacy of antidepressants

Regarding the efficacy of antidepressant medication in the treatment of minor or subthreshold depression, data, and opinions are rather controversial. One meta-analysis, conducted in 2002, did not find a significant relationship between treatment-placebo difference and severity of depression.29 However, two more recent meta-analyses reported strong associations between symptom severity at baseline and benefits of antidepressant medication over placebo.30,31 Authors suggest that “there is little evidence to support the prescription of antidepressant medication to any but the most severely depressed patients”30 and maintain that “the benefits of antidepressants may be minimal for patients suffering from mild or moderate depression.”31 However, these conclusions have been seriously challenged, a.o. in a re-analysis of the Kirsch data.31 This reanalysis used a different statistical approach, detected some flaws in Kirsch’s calculations and showed an effect size of antidepressants for depression of 0.34 with no role of baseline symptom severity. It was concluded that the efficacy of antidepressants is not restricted to a certain degree of symptom severity.32

Efficacy and tolerability of antidepressants in adult patients with minor depression have been analyzed in a meta-analysis.33 Only double blind, randomized placebo-controlled trials were included, patients with severe organic diseases were excluded. Of 719 papers screened, a total of only six studies comprising 234 patients in the antidepressant and 234 patients in the placebo arm fulfilled the inclusion criteria for this meta-analysis. In three of these studies, the selective serotonin reuptake inhibitor (SSRI) paroxetine was compared with placebo. In the other studies, fluoxetine, amitryptiline, and isocarboxazid were the active drugs. In most studies, the number of patients participating was low (three trials included less than 50 patients), and recruitment exceeded 100 patients only in two trials.34,35 Duration of treatment was 6 to 12 weeks, three studies were conducted in primary care and in two studies, patients older than 60 years were included. The authors rated the methodological quality of the included studies as relatively low. Their main finding was that antidepressants and placebo did not significantly differ in the non-response rate of patients with minor depression (antidepressants 59%, placebo 62%) and suggested that a clinically relevant superiority of antidepressants to placebo is unlikely. However, major methodical limitations such as small sample size as well as the short duration of treatment and of observation limit their conclusions.

In the meta-analysis cited above,33 the two methodically most stringent studies with a 12-week treatment period and sufficient sample size of 20435 and of 16235 patients with minor depression, both show a superiority of the antidepressant over placebo. Paroxetine (10 to 40 mg/day) showed greater symptom reduction than placebo ($P=0.004$), problem-solving treatment was not more effective than placebo.34 Judd et al found that treatment with fluoxetine is more efficacious than placebo; although the placebo-treatment difference in the improvement of the Hamilton depression rating scale was only 1.7 points.35

Two studies were not included in the meta-analysis.33 In a 12-week trial with three arms,35 the effects of St John’s wort, citalopram, and placebo were investigated in patients suffering from minor depression. Neither St John’s wort nor citalopram differed significantly from placebo regarding depressive symptoms or quality of life. In the Hamilton Depression Rating Scale (HDRS) total score, St John’s wort was less effective than placebo.

A five-arm clinical trial with a duration of 10-weeks assessed the efficacy of sertraline and cognitive-behavioral treatment in 368 patients with mild-to-moderate depression included 1099 primary care patients after screening.26 The five arms included sertraline (flexible dose up to 200 mg/day, plasma levels were monitored), placebo, group CBT, moderated self-help groups, and free choice of sertraline or CBT. HDRS improvement in the sertraline arm was significantly larger than in the placebo arm (6.8 points vs 4.5 points), improvement in CBT (6.7 points) was significantly larger compared with the guided self-help groups (1.9 points) but not compared with placebo (4.5 points). Sertraline-placebo difference in efficacy was particularly pronounced in patients with very mild depression.

In a 1-year follow-up study, patients with sertraline treatment and those with CBT treatment did not differ
in recovery, i.e., the number of weeks in the follow-up period without symptoms (sertraline: 32+/−24 weeks, CBT: 28+/−24 weeks). Of clinical interest is also a 52-week pragmatic long-term trial in primary care patients with minor or mild-major depression. They were randomized into two groups, namely consultations within 3 months of usual care plus paroxetine or usual care alone. No differences in effectiveness between both treatment groups were found, patients with antidepressant medication were slightly more satisfied with their treatment.

In this context, the robust efficacy of antidepressants in the treatment of dysthymia, which is phenomenologically similar to minor depression, but different in the chronic course of illness, should be noted. Psychopharmacological therapy was found to be effective in numerous studies (for example, refs 34, 38) and a Cochrane review recommended antidepressants as first treatment in dysthymia.

The fundamental problem of blinding patients and therapists to treatments in trials comparing psychotherapy to control conditions has been mentioned above. Cuijpers et al investigated the effects of blinding on the outcomes of psychotherapy and pharmaceutical therapy for adult depression and found that studies in which both groups of patients (and therapists) are not blinded result in a “very small, but significantly higher effect for pharmaceutical therapy.” This finding is in contrast to an earlier meta-analysis of studies directly comparing psychotherapy and pharmaceutical therapy in which no difference was observed.

Simon et al evaluated 19,751 patient records from four large US American health care systems and concluded “that prescription of antidepressant medication for minimal or mild depression is much less common than suggested by previous reports.” Therefore, the assumption that antidepressants are overprescribed for patient suffering from non-major depression does not appear to be justified.

In conclusion, randomized studies on the efficacy of antidepressants in minor depression indicate superiority over placebo. This result is particularly supported by newer, well-controlled trials.

Patient preferences

One issue of major relevance in clinical practice, but somewhat neglected in research, is the patient’s preference regarding treatment. There is wide agreement that the majority of patients prefer psychotherapy over antidepressant medication. Antidepressants are often regarded as addictive and psychotherapy is assumed to solve the cause of the depression. Therefore, in clinical practice, most psychiatrists try to convince only their severely depressed and suicidal patients about the efficacy of antidepressants, while patients with minor/subthreshold depression are treated according to their preference.

Research on the relevance of patients’ preference in the treatment of depression is scarce and controversial. A review conducted in 2004 reported that in two patient-preference trials, preference did not influence treatment outcome. However, in two more recent trials, the findings were different: patients who were assigned to their preferred treatment were found to be more often compliant and had better clinical outcomes. The other trial showed that depressed patients receiving their preferred treatment (n=36), whether sertraline or CBT, responded better than those who did not receive their preferred therapy (n=54, P=0.001); effect size of the differences between matched and mismatched patients was 0.42.

The controversy regarding the importance of preference, as reported in two positive and two negative trials, might be explained by methodological problems. The majority of patients with a strong preference for psychotherapy might not enter a clinical trial in which they have any “risk” of being treated with an antidepressant. This problem is particularly relevant for patients with minor/subthreshold depression who may be particularly opposed to pharmaceutical treatment.

In clinical practice, patient preferences should be taken into account in a shared decision-making process. A recent review indicates its benefits in terms of adherence, satisfaction with care, and outcome.

Is the efficacy of antidepressants in the treatment of minor depression clinically relevant?

The NICE guidelines proposed a drug-placebo difference of at least 3 points regarding the improvement in the Hamilton-Depression rating scale-17 total score as the threshold for clinical significance. As mentioned before, this difference has not been reached in any clinical trial. However, of the three methodologically most
stringent investigations, all found a significant difference: using the HDRS, Judd et al.\textsuperscript{15} of 1.7 points and Hegerl et al.\textsuperscript{26} of 2.3 points. Williams et al.\textsuperscript{34} used the Hopkins Symptom Checklist Depression scale and found a difference of 0.21 points, which after transformation is equivalent to about 2.5 HDRS points.

The question arises whether it is justified to assess the threshold of clinically relevant efficacy on the basis of an arbitrary antidepressant-placebo difference, reported in randomized clinical trials. This is thoroughly discussed by Hegerl et al.\textsuperscript{25} who argue that the clinical relevance or effectiveness of antidepressants cannot be drawn from intent-to-treat and last-observation carried over approaches. Moreover, in contrast to RCTs, antidepressants in clinical practice allow individually tailored treatment regarding the drug selected (eg, sedating vs non-sedating), dosage in case of tolerability problems or insufficient efficacy, and administration of augmentation or combination strategies.

The argument that antidepressants’ efficacy is similar or not much stronger than “only placebo” is based on weak evidence only and also misleading. It is wellknown that a placebo has pronounced effects on symptoms due to expectation and conditioning. The placebo effect may be enhanced by a positive physician-patient relationship as it involves three components: acknowledgement of the patient’s difficulties by paying attention to his/her problem, a credible therapeutic ritual and the patient-perceived quality of the relationship with the psychiatrist. Antidepressants exert an effect not only because of their pharmacology, but because a prescription can be expected to provide these components.

A small overall difference between antidepressant and placebo does not exclude that there are single patients with a strong positive response. Particularly patients with markedly disturbed sleep, who might be at risk to develop a dependence on sleep medication, often strongly benefit from a sedating antidepressant.

**Conclusion**

The doubt about the efficacy of antidepressants in patients with minor/subthreshold depression is not justified. In contrast to the results of older and methodologically less solid reviews and meta-analyses, newer studies found a significant advantage over placebo. Studies also show that antidepressants are at least equal to psychotherapy in reducing depressive symptoms and both treatments are better than usual care.

In order to define a clinically relevant treatment effect, more effectiveness rather than efficacy studies are needed, which include effects sizes and after treatment an observation period of 6 to 12 months. Moreover, outcomes are still defined in terms of classical expert-rated symptoms only, rather than by patient-reported outcomes such as health-related quality of life.

One major advantage of antidepressant treatment is its immediate availability (together with rather low costs) and the short time span (within 2 to 3 weeks) in which knowledge about the effects of the treatment is available. Risks or disadvantages of a probationary antidepressant treatment are limited. In contrast, psychotherapy is often not readily accessible, time-intensive and frequently associated with a long waiting period.

In order to identify an appropriate treatment for the individual patient, patients should be well informed about treatment options, their preferences should be explored, and shared decision-making should be introduced with the aim to ensure patient participation and compliance.

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Dissociation debates: everything you know is wrong
Richard J. Loewenstein, MD

Introduction

The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), defines dissociation as a disruption, interruption, and/or discontinuity of the normal, subjective integration of behavior, memory, identity, consciousness, emotion, perception, body representation, and motor control.

The DSM-5 dissociative disorders (DD) are:

1. Dissociative Identity Disorder (DID);
2. Dissociative Amnesia (DA);*
3. Depersonalization/Derealization Disorder (DPDRD);
4. Other Specified Dissociative Disorders (OSDD);
5. Unspecified Dissociative Disorder (UDD).

*In DSM-5 Dissociative Fugue (DF) is now a subtype of Dissociative Amnesia (DA), and not a separate disorder.

The DSM-5 diagnostic criteria for Posttraumatic Stress Disorder (PTSD) now include a Dissociative Subtype (PTSD-DS). Dissociative amnesia as a symptom is a diagnostic criterion for both DID and for PTSD. Criteria for PTSD-DS are that reminders of the traumatic event are associated with dissociative symptoms, and that the dissociative symptoms are not better accounted for by another mental disorder.

Controversy about dissociation and the dissociative disorders (DD) has existed since the beginning of modern psychiatry and psychology. Even among professionals, beliefs about dissociation/DD often are not based on the scientific literature. Multiple lines of evidence support a powerful relationship between dissociation/DD and psychological trauma, especially cumulative and/or early life trauma. Skeptics counter that dissociation produces fantasies of trauma, and that DD are artefactual conditions produced by iatrogenesis and/or socio-cultural factors. Almost no research or clinical data support this view. DD are common in general and clinical populations and represent a major underserved population with a substantial risk for suicidal and self-destructive behavior. Prospective treatment outcome studies of severely ill DD patients show significant improvement in symptoms including suicidal/self-destructive behaviors, with reductions in treatment cost. A major public health effort is needed to raise awareness about dissociation/DD, including educational efforts in all mental health training programs and increased funding for research.

Keywords: amnesia; controversy; dissociation; dissociative disorder; dissociative identity disorder; dissociative theoretical model; trauma

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(email: rloewenstein@sheppardpratt.org)
PTSD Criterion A traumatic stressor lead to depersonalization/derealization symptoms. In DSM-5, the DD section is specifically placed after the Trauma-and-Stressor Related Disorders to show their relationship to traumatic experiences.1

Since first systematically described in the early 19th century, dissociative disorders and dissociation have been entangled not only in professional debates, but in controversies within the social, political, and cultural zeitgeist. The history of dissociation and dissociative disorders traverses the modern history of psychiatry and has been central to some of its most complex and controversial disputes.2,3 The dissociation debate centers on whether dissociation/DD are fundamentally related to psychological trauma or artefactually created conditions, with confabulated trauma memories.2

Few mental health training programs educate about dissociation and the diagnosis and treatment of DD. In the author’s experience, many clinicians, researchers, journalists, and members of the public have beliefs about dissociation/DD founded on unexamined ideas and influenced by media portrayals. Often, both sceptical and naively credulous views of DD appear to be based on the media portrayal, not the scientific literature.

The Trauma Model (TM)

The Trauma Model posits that dissociation is a psychobiological state or trait that functions as a protective response to traumatic or overwhelming experiences.4 Dissociation is most commonly conceptualized as a continuum from normal to pathological, with states of intense absorption, like spacing out while driving and missing an exit at one end, and severe dissociative disorders like DID at the other. Research supports an alternative: the Taxon Model positing two continua: normal and pathological dissociation.5 The latter comprises a distinct group of highly traumatized individuals—about 3.5% of the general population—who endorse a specific cluster of symptoms consistent with severe dissociative psychopathology such as DID. These include severe depersonalization, recurrent amnesia for current experiences, and identity alteration.5 Dissociative symptoms, such as dissociative amnesia and depersonalization/derealization have been described trans-diagnostically.2,6 Confusingly, the same terms used to describe these dissociative symptoms, are used for specific DD, such as DID, DA, and DP-DRD. In this review, the abbreviations DA and DP-DRD will be used when referring to the disorders; otherwise, the terms refer to symptoms.

The TM posits that dissociation mitigates the impact of trauma by psychobiologically sequestering information about trauma through protective activation of altered states of consciousness. Subsequently, dissociation segregates from ordinary awareness the full meaning and impact of traumatic events for the person.2 There are empirically supported treatment models for severe DD, consistent with the TM.7,8 Contrary to popular and skeptical belief, these do not prioritize “hypnosis for memory recovery” (see below).5,10 Severely ill DD patients’ symptoms are usually markedly exacerbated by a sole focus on traumatic memories, often requiring inpatient hospitalization for stabilization.7,10 TM treatment models emphasize safety from suicidal and self-destructive behaviors, and stabilization of uncontrolled, overwhelming dissociative state shifting and PTSD intrusions.2,7,10 Hypnosis is used primarily to help patients contain and modulate severe symptoms.2,7

Skeptical views of dissociation and dissociative disorder

Skeptics view DD as an unscientific fad of the 1980s.9,12 They propose three interrelated models to support this idea. In the Iatrogenic Model (IM) DID is viewed as a condition produced in highly hypnotizable, “fantasy-prone,” “suggestible” patients—many with Borderline Personality Disorder (BPD)—by clinicians who believe in “repressed memories” and “multiple personalities” using “risky” treatments like hypnosis for “recovered memory therapy” to exhume forgotten traumas as the primary treatment goal, but instead “implant” false memories.2,5,10 “Fantasy-prone” is a specific construct from hypnosis and cognitive research, describing non-clinical samples of highly hypnotizable individuals with the ability to generate an extraordinarily vivid, compelling fantasy life with cognitive slippage and difficulty discerning the difference between internal and external experience. This dissociation “epidemic” is based on “Freudian” ideas of complete repression of traumatic memories, that are revealed under hypnosis.9 The Sociocognitive Model (SCM) posits that psychotherapy is not necessary for the development of severe DD. North American culture—with its media focus on childhood
sexual abuse, “repressed memories”, and “multiple personalities”—is sufficient to cause highly suggestible people to develop the belief that they have dissociative conditions.13 The Fantasy Model (FM) conceptualizes dissociation as a cognitive trait that leads to fantasies/confabulations of traumatic experiences.14

Proponents of the IM/SCM/FM claim that minimal data support the relationship of trauma and dissociation.9,13 They posit that there are no psychological processes to explain amnesia for trauma, that traumatic experiences “are remembered too well.”12 Treatment involves ignoring the DD and trauma symptoms, debunking the false memories, focusing on “everyday” problems, reunification with “falsely accused” family members, and treatment of “real” psychiatric disorders such as depression.12 In this view, the “decline” of the DD after the 1980s was the typical course of a fad.9

What does the historical record tell us?

DD are among the oldest reported psychiatric disorders with case reports appearing at the end of the 18th century and extensive descriptions in the medical literature of the 19th century.3 Nineteenth-century controversies included whether hysteria should be conceptualized as dual consciousness (dissociation), somnambulism (ie, hypnotic states), or hysteria (somatoform symptoms).2,3 Ultimately, somatoform hysteria became the unifying framework for all these conditions.2,3 Nineteenth-century controversies about hysteria parallel modern ones. Was hysteria related to psychological trauma—including sexual trauma? Was it due to frustrated and/or repressed sexuality in women, or female sexual overindulgence? Was it an artifact of suggestion on impressionable women?2,3

Charcot/Babinski/Janet/Freud

Neurologist Jean-Martin Charcot’s work with impoverished hysterical patients at La Salpêtrière Hospital in Paris from the 1860s to his death in 1893 has become a part of the cultural history of psychiatry.2,3,15 Charcot viewed hysteria as a neurological disease but later posited psychological and posttraumatic factors as etiological. He viewed hypnotic susceptibility as a core feature of hysteria.2,3,11 After Charcot’s death, Josef Babinski replaced Charcot at La Salpêtrière, and defined hysteria (and dissociation) as produced by “suggestion,” ameliorated by “persuasion,” and exacerbated by hypnosis.2,3 Since then, the generally accepted historical view has been that Charcot’s patients were highly suggestible women and that most of their hysterical symptoms were an artefactual production of the setting and social demands to perform for Charcot.2,3,15,16 They are believed to have disappeared by the end of 19th century.2,3,15,16

Pierre Janet, also at La Salpetrière, viewed traumatic experiences as central to hysterical and dissociative phenomena, and developed a conceptual and psychotherapeutic model whose basic elements are similar to the modern TM.2,3,17 Sigmund Freud was influenced by Charcot and, early on, by Janet.2,3 Contrary to the IM/SCM/FM attributions, Freud renounced the idea that repressed memories of childhood sexual trauma caused hysteria, ascribing these memories to Oedipal fantasies.2,3 Early on, he eschewed hypnosis, as have his followers. Many contemporary psychoanalysts express skepticism about trauma-based conceptualizations of dissociation.18

Historical research

Charcot’s patients

Historical research on the medical records of Charcot’s patients at La Salpêtrière support the TM.19,20 This has documented extreme early and later life sexual, physical, medical and emotional trauma, injuries from serious accidents, sexual exploitation, massive traumatic losses, neglect, deprivation, and social marginalization among these impoverished women.19,20 Many were also likely affected by wartime trauma, including the shelling of Paris in 1870 during the Franco-Prussian War, and exposure to the urban street battles, summary executions, and bombing of Parisian working class neighborhoods during the Paris Commune in May, 1871.19,20

Wartime trauma and dissociation

Until the latter part of the 20th century, except during wartime, there was decreased professional attention to dissociation, with the dissociative conditions seen as rare and exotic.2 Babinski’s theories lost many followers when all hysterical and dissociative symptoms were found in the battlefield (“shell shock”) casualties of World War I.2,3 In every subsequent war, psychogenic (dissociative) amnesia, fugue, depersonalization/derealization, hysterical (somatoform), and in modern studies, significant rat-
ing-scale elevations in dissociative symptoms have been reported in case series and systematic, international studies of soldiers in the immediate aftermath of combat, or as part of posttraumatic disorders related to war. This includes World War II, the Korean War, the Vietnam War, the 6-day Arab-Israeli War, Iran-Iraq War, the Gulf War, and Iraq and Afghanistan Wars. Dissociative symptoms, such as amnesia, have also been reported in survivors of the European and Cambodian Holocausts, in refugees and survivors of torture, and among many other traumatized populations.

Modern interest in dissociation and dissociative disorders

Modern study of dissociation results from several factors. Systematic, psychiatric attention to childhood maltreatment began in the 1960s with the description of the “Battered Child Syndrome” in 1962. In the 1970s, feminist scholars, psychiatrists and psychologists debunked the Freudian theory that reports of childhood sexual abuse were primarily based in oedipal fantasies. In 1980, the DSM-III added the diagnosis of PTSD—with psychogenic amnesia as a criterion symptom—discarded the term hysteria and created diagnostic categories for Somatoform and Dissociative Disorders. After the publication of the DSM-IV, the terms Psychogenic Amnesia and Psychogenic Fugue were replaced by Dissociative Amnesia (DA) and Dissociative Fugue (DF), respectively. Multiple Personality Disorder (MPD) was replaced by Dissociative Identity Disorder (DID). Returning Vietnam veterans brought wartime trauma and the diagnosis of PTSD into psychiatric and cultural awareness.

Rigorous research on hypnosis in the 1950s and 1960s began to move hypnosis into the mainstream of psychology and psychiatry. The publication of Sylva in 1976, and the subsequent television and movie productions based on it, ignited public interest in what was then known as Multiple Personality Disorder, although this has been cited by skeptics as part of the social contagion producing DID.

Modern skepticism about dissociation and dissociative disorders

In the early 1990s, skeptical views of dissociation and DD emerged with the rise of “False Memory Syndrome” (FMS), supported by an organized group, many of whose members had been “accused” – some in the courts - by their children of childhood sexual abuse, and academics and clinicians who supported them. An extensive, highly publicized backlash occurred with promulgation of a legal theory where “recanting” former patients and/or “accused” parents sued mental health providers for malpractice and/or alienation of affections, alleging that the clinicians “implanted” false memories of childhood sexual abuse and created iatrogenic DD diagnoses. A cadre of attorneys and their experts divided up the country, seeking plaintiffs to bring these suits in local jurisdictions.

This legal theory was a counterpoint to a theory that survivors of childhood abuse could sue perpetrators outside the statute of limitations if they had completely “repressed” memories of abuse, and only recollected them later on, although dissociative autobiographical memory disturbances are often characterized by partial and/or fragmented recall. “False-memory” views continue to have considerable following in standard psychology textbooks, the media, and among many mental health professionals.

In fact, False-Memory Syndrome as a clinical construct has never been operationalized, studied, or validated. Only one study investigated the clinical characteristics of “retractors” of abuse allegations. These patients had significant personality disorders and embraced the victim role, looking externally for explanation of their problems: first by “accusing” their parents, sometimes through lawsuits, and, subsequently, by suing their clinicians. Retractors had long psychiatric histories, including documented PTSD, somatoform, dissociative, and factitious symptoms. In treatment, most dissociative and posttraumatic symptoms had improved, but the characterological issues had not been adequately addressed.

What are the data on dissociation and dissociative disorders?

Scientific study of dissociation

Beginning in the 1980s, researchers on dissociation and DD developed a number of reliable and valid symptom self-report inventories, structured and semi-structured diagnostic interviews, and self-report diagnostic inventories to assess state and trait dissociation and DD in children, adolescents, and adults (See ref 2 for
a full review). Use of these measures, in international clinical and general population samples in the USA, Canada, China, Europe, Latin America, Japan, Korea, Israel, Turkey, Taiwan, Australia, and New Zealand (among others) have identified cross-cultural samples of individuals with DD. Measures include the Dissociative Experiences Scale (DES), the DES-Taxon Scale (DES-T), the Adolescent DES (A-DES), the Dissociative Disorders Interview Schedule (DDIS), the Clinician Administered Dissociative States Scale (CADSS), and the Structured Clinical Interview for DSM Dissociative Disorders (SCID-D).

In these studies, higher dissociation scores and/or a DD diagnosis were strongly linked to acute and/or chronic traumatic experiences. In retrospective, prospective, international, cross-cultural studies of traumatized populations—including children, adolescents, and adults—greater trauma severity and chronicity is generally associated with increased dissociative symptoms, higher dissociation scores on standard measures, and a diagnosis of a DD. Studies have included victims of childhood maltreatment and/or neglect, adult rape, combat, prisoner-of-war (POW) experiences, torture, trafficking, genocide, civilian dislocation during wartime, repeated painful medical procedures, accidents, and natural disasters. Studies show that earlier and cumulative trauma, as well as early life attachment pathology, particularly Disorganized (Type D) Attachment strongly predict elevated dissociation scores on standardized measures in later life, and/or development of a DD.

Epidemiological studies

General population studies

Random samples of the general population in Canada and Turkey (female sample, 50% of whom were illiterate) found a life-time prevalence of DD of 12.2% and 16.3% respectively. A general population study in New York State found a 1-year prevalence of 9.1% for the DD. In Canada and New York, prevalence of DD was 1.3% and 1.5% of the population. In Turkey, the lifetime prevalence of DD was 1.1% and the prevalence of DSM-IVTR Dissociative Disorder Not Otherwise Specified (DDNOS) “with multiple personality states” was 4.1%. The DSM-5 diagnostic criteria for DID were modified to decrease DDNOS diagnoses. Under DSM-5 diagnostic criteria, the prevalence of DID in this sample of Turkish women could be higher than 1.1% (Table I).

A large, prospective Finnish general population study found a point prevalence for “pathological dissociation,” as measured by the DES-T, of about 3.5%, initially and at 3-year follow-up. Higher dissociation scores were significantly associated with depression and suicidality. Conventional belief associates dissociation with female sex. In this study, males and females did not differ on rates of pathological dissociation. A large international WHO study found that the Dissociative PTSD Subtype was found more commonly in males. In a related study of a large sample of Finnish adolescents, 5.5% had the highest scores on the A-DES. High A-DES scores characterized a group with higher rates of self-injury, substance and alcohol abuse, smoking, poor school performance, and social isolation. Studies in military, clinical, and nonclinical samples have found a strong relationship between dissociation and suicidal and self-destructive behaviors, even after controlling for the known relationship between self-destruction and childhood and adult trauma.

Studies of DD in clinical populations

In clinical populations, international epidemiological studies in North America, Europe, the Middle East, and Asia show that DD are readily found in adolescent, adult inpatient, residential, outpatient, substance abuse, and emergency department populations. In most of these studies, probable DD patients were identified by using the DES or A-DES for screening. DD diagnoses were established by administering diagnostic interviews to patients scoring above a specific DES cutoff score. In these clinical studies, DD prevalence ranged from 4.6% to 46% across diverse samples (eg, private, community, state hospital), with DID from 0.4% to 14%.

These epidemiological studies do not fit the IM/SCM/FM paradigms. Few subjects had previously been recognized as having a DD or were in specialized DD psychotherapy. They were identified by reliable and valid screening and diagnostic inventories. Several US samples were drawn from state hospitals or university clinics for impoverished chronically mentally ill patients. Subjects from Turkey or China would have had little exposure to North American media depicting DD.
Psychobiology of dissociation

A number of lines of evidence support conceptualizing dissociation as the human equivalent of the animal “freeze” or “feigning death,” protective response in the face of life-threatening danger, where fight/flight has failed or would be more dangerous.2,48 Autonomic changes may include a decrease or no change in blood pressure, heart rate, heart rate variability, lowered skin conductance, and decrease in skeletal muscle tone.2,48 The polyvagal theory of Stephen Porges posits that, as fight-flight sympathetic stress responses fail, dominance by the primitive vagal parasympathetic system results, leading to the freeze response.49 This may result in a shut-down state characterized by dense trance, increase in pain threshold, and stupor – even to the extent of catatonic-like nonresponding.2,48

Genetic, developmental, neurobiological and psychophysiological studies have supported a model

<table>
<thead>
<tr>
<th>Study</th>
<th>Winnipeg, Canada</th>
<th>New York State, USA</th>
<th>Sivas, Turkey</th>
<th>Kuipio, Finland</th>
<th>Kuipio, Finland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measures</td>
<td>DES and DDIS</td>
<td>DES, SCID-D, SCID-II, GAF</td>
<td>DDIS, SCID-PTSD, and SCID-II</td>
<td>DES, DES-T, BDI, TAS, SDQ*, ACE</td>
<td>A-DES, YSR, Drug/Etoh History Scale for NSSI</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>502</td>
<td>658</td>
<td>628 (female)</td>
<td>20011, 1497 (2008)</td>
<td>1585*</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Subjects (%)</td>
<td>Subjects (%)</td>
<td>Subjects (%)</td>
<td>Subjects (%)</td>
<td>Subjects (%)</td>
</tr>
<tr>
<td>Pathological Dissociation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissociative amnesia</td>
<td>6.0</td>
<td>1.8</td>
<td>7.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissociative fugue</td>
<td>0</td>
<td>0</td>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissociative identity disorder</td>
<td>1.3</td>
<td>1.5</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depersonalization disorder</td>
<td>2.8</td>
<td>0.8</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissociative disorder not otherwise specified (NOS)</td>
<td>0.2</td>
<td>4.3</td>
<td>8.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dissociative disorder NOS with multiple personality states</td>
<td></td>
<td></td>
<td></td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Dissociative disorder NOS with indirect cues for personality states</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.4</td>
</tr>
<tr>
<td>Derealization without depersonalization</td>
<td></td>
<td></td>
<td></td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Dissociative trance disorder</td>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All dissociative disorders</td>
<td>12.2</td>
<td>9.1</td>
<td>18.3</td>
<td>5.5 (highest dissociation)</td>
<td></td>
</tr>
</tbody>
</table>

Table I. Dissociative Disorders in the General Population. Adapted from Loewenstein et al (2017).2 ACE, Adverse Childhood Experiences Scale; A-DES, Adolescent Dissociative Experiences Scale; BDI, Beck Depression Inventory; DDIS, Dissociative Disorders Interview Schedule; DES, Dissociative Experiences Scale; DES-T, DES Taxon Scale; GAFS, Global Assessment of Functioning Scale; SCID-D, Structured Clinical Interview for DSM-IV-TR Dissociative Disorders; SCID-PTSD; Structured Clinical Interview for DSM-IV-TR PTSD; SCID-III, Structured Clinical Interview for DSM-IV-TR Axis II Personality Disorders; SDQ, Somatoform Dissociation Scale; TAS, Tellegen Absorption Scale; YSR, Youth Self Report
where repeated chronic trauma, often in the setting of captivity, e.g., childhood maltreatment, intimate partner violence (IPV), and/or trafficking experiences, may lead to a preferential freezing/dissociative response to threat. In a study of 298 rape victims seen in a specialized emergency clinic within 1 month of the rape, 70% reported tonic immobility (TI), and 48% an extreme tonic immobility response during the rape. Women with a history of childhood or adult sexual assault were twice as likely to report tonic immobility. TI predicted the development of PTSD and depression. TI subjects reported high rates of detachment from themselves and/or the rape, as well as numbness and lack of pain perception.

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion Rate</th>
<th># approached</th>
<th>Diagnostic Instrument</th>
<th>DES cutoff</th>
<th>DID</th>
<th>All DD</th>
<th>Mean DES</th>
<th>SD DES</th>
<th>&gt; DES&lt;sup&gt;(a)&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inpatient Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ross et al (Canada) 1991&lt;sup&gt;75&lt;/sup&gt;</td>
<td>61.8%</td>
<td>484</td>
<td>DDIS</td>
<td>20</td>
<td>5.4%</td>
<td>20.7%</td>
<td>14.6</td>
<td>14.2</td>
<td>30.1%</td>
</tr>
<tr>
<td>Saxe et al (USA) 1993&lt;sup&gt;76&lt;/sup&gt;</td>
<td>64.0%</td>
<td>172</td>
<td>DDIS</td>
<td>25</td>
<td>4.0%</td>
<td>13.0%</td>
<td>—</td>
<td>—</td>
<td>15.0%</td>
</tr>
<tr>
<td>Latz et al (USA) 1995&lt;sup&gt;77&lt;/sup&gt;</td>
<td>99.0%</td>
<td>176</td>
<td>DDIS</td>
<td>—</td>
<td>12%</td>
<td>46%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Modestin et al (Switzerland) 1996&lt;sup&gt;78&lt;/sup&gt;</td>
<td>207</td>
<td>DDIS</td>
<td>—</td>
<td>0.4%</td>
<td>5.0%</td>
<td>13.7</td>
<td>13.5</td>
<td>12.0%</td>
<td></td>
</tr>
<tr>
<td>Rifkin et al (USA) 1998&lt;sup&gt;79&lt;/sup&gt;</td>
<td>63%</td>
<td>150</td>
<td>SCID-D</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tutkun et al (Turkey) 1998&lt;sup&gt;80&lt;/sup&gt;</td>
<td>63.6%</td>
<td>166</td>
<td>DDIS</td>
<td>30</td>
<td>5.4%&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>10.2%&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>17.8</td>
<td>14.9</td>
<td>14.5%</td>
</tr>
<tr>
<td>Friedl et al (Netherlands) 2000&lt;sup&gt;81&lt;/sup&gt;</td>
<td>50.4%</td>
<td>122</td>
<td>SCID-D</td>
<td>25</td>
<td>2.0%</td>
<td>8.0%</td>
<td>20.0</td>
<td>18.1</td>
<td>29.5%</td>
</tr>
<tr>
<td>Ross et al (USA) 2002&lt;sup&gt;82&lt;/sup&gt;</td>
<td>51.6%</td>
<td>407</td>
<td>DDIS</td>
<td>—</td>
<td>7.5%</td>
<td>40.8%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lipsanen et al (Finland) 2004&lt;sup&gt;83&lt;/sup&gt;</td>
<td>—</td>
<td>39</td>
<td>DDIS</td>
<td>—</td>
<td>21.0%</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Ginzburg et al (Israel) 2010&lt;sup&gt;84&lt;/sup&gt;</td>
<td>84.0%</td>
<td>120</td>
<td>SCID-D</td>
<td>—</td>
<td>0.8%</td>
<td>12.0%</td>
<td>20.9</td>
<td>18.7</td>
<td>—</td>
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<tr>
<td>Yu et al (China) 2010&lt;sup&gt;85&lt;/sup&gt;</td>
<td>96.0%</td>
<td>569</td>
<td>DDIS</td>
<td>Weighted&lt;sup&gt;(c)&lt;/sup&gt;</td>
<td>0.53%&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>15.3%&lt;sup&gt;(a)&lt;/sup&gt;</td>
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<td>Sar et al (Turkey) 2003&lt;sup&gt;86&lt;/sup&gt;</td>
<td>81.5%</td>
<td>150</td>
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<td>30</td>
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<td>240</td>
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<td>25</td>
<td>2.5%</td>
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<td>Lipsanen et al (Finland) 2004&lt;sup&gt;88&lt;/sup&gt;</td>
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<td>39</td>
<td>DDIS</td>
<td>—</td>
<td>14.0%</td>
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<td>Foote et al (USA) 2006&lt;sup&gt;89&lt;/sup&gt;</td>
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<td>82</td>
<td>DDIS</td>
<td>—</td>
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<tr>
<td>Sar et al (Turkey) 2014&lt;sup&gt;90&lt;/sup&gt; adolescents</td>
<td>62.9%</td>
<td>116</td>
<td>SCID-D</td>
<td>N/A</td>
<td>16.4%</td>
<td>45.2%</td>
<td>(A-DES)&lt;sup&gt;(d)&lt;/sup&gt;</td>
<td>2.8</td>
<td>42.4%&lt;sup&gt;(d)&lt;/sup&gt;</td>
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<td>Emergency Ward</td>
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<tr>
<td>Sar et al 2007&lt;sup&gt;91&lt;/sup&gt; (Turkey)</td>
<td>44.3%</td>
<td>43</td>
<td>SCID-D</td>
<td>25</td>
<td>14.0%</td>
<td>34.9%</td>
<td>23.4</td>
<td>19.3</td>
<td>39.5%</td>
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<td><strong>Substance Abuse</strong></td>
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<td>—</td>
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<td>DDIS</td>
<td>—</td>
<td>14%</td>
<td>39%</td>
<td>17.8</td>
<td>14.4</td>
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<td>215</td>
<td>SCID-D &amp; DDIS</td>
<td>30</td>
<td>2.8%</td>
<td>17.2%</td>
<td>24.5</td>
<td>17.5</td>
<td>36.7%</td>
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**Table II.** Prevalence of dissociative disorders in psychiatric samples (Adapted from Sar, 2011<sup>39</sup>). DES (Dissociative Experiences Scale) DDIS (Dissociative Disorders Interview Schedule) SCID-D (Structured Clinical Interview for DSM-IVTR Dissociative Disorders). (a) Clinically confirmed diagnosis. (b) Percentage of patients with dissociative experiences scale (DES) score above cutoff point (1-100 scale). (c) Weighted average of patients with DES cutoff 0-10, 11-20, 21-40, >41. (d) The A-DES is scored on a 1-10 scale; cutoff point 3.0.
The Dissociative Subtype of PTSD (PTSD-DS) has been identified in many traumatized populations, including large international samples, and may comprise 15% to 30% of individuals with PTSD. In fMRI studies, PTSD-DS subjects, in contrast those with non-dissociative PTSD, respond to personal trauma scripts with depersonalization/derealization and hypomotility, not flashbacks, and hyperarousal. PTSD-DS subjects show patterns of increased brain activation of frontal systems (medial and/or ventral pre-frontal cortex, dorsal anterior or cingulate) and decreased activation of amygdala and insula. They show a pattern of decreased or no change in blood pressure and heart rate associated with these neural network patterns.

Similarly, in response to aversive stimuli, Depersonalization/Derealization Disorder patients demonstrate inhibition of limbic arousal by increased activation of frontal systems along with autonomic blunting. Studies in clinical and nonclinical populations have identified neural network patterns associated with Dissociative Amnesia (DA) and Dissociative Fugue (DF) that involve top-down inhibition by frontal systems of hippocampal, temporal and occipital lobe areas involved in autobiographical memory.

PET and fMRI studies of DID patients found that self-states subjectively experiencing traumatic memory scripts as personal autobiographical memory (Traumatic Identity State-TIS) showed patterns of limbic system activation and decreased activity in frontal systems similar to non-dissociative PTSD patients, as well as autonomic changes typical of sympathetic hyperarousal. Neutral Identity States (NIS) did not report experiencing trauma scripts as autobiographical memory. NIS showed brain and psychophysiological responses similar to PTSD-DS. Simulating controls had markedly different brain activation and psychophysiological patterns from DID patients.

In an MRI study, women with DID had significantly reduced hippocampal and amygdalar volumes compared to healthy controls. Many studies have shown a relationship to trauma and reduced hippocampal volume, especially to chronic trauma, thought to be related to the impact on the hippocampus of repeated release of glucocorticoids. Studies of amygdala volume in maltreated children and adults with a history of childhood adversity show that early, cumulative trauma, as reported by most DID patients, predicts stress-related reduction in amygdalar volumes, hypothesized as also due to the impact of repeated glucocorticoid release.

Genetic studies

Genetic studies of dissociation suggest that there is a complex interplay between genetic factors and type, timing, and chronicity of trauma. Studies comparing child and adult cohorts of adoptive siblings, fraternal and identical twins suggest that genetics account for around 50% of the interindividual variance in dissociative symptoms, with “non-shared,” stressful environmental experiences accounting for most of the additional variance. Studies have linked dissociation to the interaction of traumatic experiences with specific single nucleotide polymorphisms in genes related to the HPA axis (FKBP5), serotoninergic (5-HTTLPR), dopaminergic (COMT) and BDNF systems.

Gene by adversity interactions have been described for FKBP5, an endogenous regulator of the stress-neuroendocrine system, conferring risk for a number of psychiatric disorders including major depressive disorder, PTSD, and for dissociation. In a prospective study of 279 maltreated and 171 non-maltreated low socioeconomic-group adolescents, significant interactive effects were found between scores on the Adolescent Dissociative Experiences Scale (A-DES), the developmental timing and chronicity of prior maltreatment, and the CATT haplotype of the FK506 binding protein 5 gene (FKBP5). The children in the study had been extensively screened at school age for maltreatment. In adolescents with no copies of the CATT haplotype, higher dissociation scores were significantly related to chronic maltreatment of early childhood onset, compared with adolescents with later onset and less chronic maltreatment, and non-maltreated adolescents.

Studies of acute dissociative responses to trauma

Depersonalization/derealization symptoms are strongly associated with acute traumatic events including motor vehicle accidents and other forms of life-threatening danger. Peritraumatic dissociation, including depersonalization/derealization, tunnel vision, trance-like experiences, confusion, changes in time-sense, disorientation, and amnesia are significantly correlated with later development of PTSD.
capable stressors–based on American POW experiences in wartime–include days of semi-starvation, exhaustion, sleep deprivation, lack of control over hygiene and bodily functions, abusive interrogations, hooding, and lack of control over movement, social contact, and communication. SERE trainees showed significant differences between pretest and posttest scores on the Clinician Administered Dissociative States Scale (CADSS) with the greatest effects for depersonalization/derealization items. Higher dissociation scores were associated with poorer performance and significantly correlated with lower cortisol levels. The cortisol/dissociation finding supports the model that dissociation is related to decreased activation of the sympathetic stress system. Similar results were found in Norwegian naval cadets undergoing a POW simulation experience, and soldiers undertaking the grueling Combat Diver Qualification Course.

**Delayed recall of traumatic events - Dissociative Amnesia**

Based on the controversies over “recovered memory,” many clinicians, members of the media, and the public disbelieve that there can be delayed recall of previously experienced traumatic events. Over 70 studies in clinical and nonclinical populations have documented amnesia for traumatic events. These include prospective studies, retrospective studies, studies of acutely traumatized soldiers after combat, victims of torture and genocide, and studies describing adults who fail to recall childhood traumas documented in their medical and/or social service records. In a study of over 9000 members of a large HMO participating in the Adverse Childhood Experiences Study (ACE Study) researchers found that the extent of childhood autobiographical memory disturbance—defined as inability to recall large aspects on one’s childhood after age 4—was directly correlated with cumulative childhood adversities, particularly sexual abuse, physical abuse, and combined physical and sexual abuse.

Another received idea is that delayed recall of trauma predicts confabulated pseudomemories. Comprehensive literature reviews have found no difference in accuracy between trauma memories with delayed or continuous recall. Proponents of the IM/SCM/FM rightly critique the commonly held naïve view that amnesia for trauma is entirely related to the severity of the trauma. Many survivors of the European Holocaust had relatively low dissociation scores on the DES and relatively low scores on amnesia on standardized PTSD or dissociation inventories, although some Holocaust survivors endorsed dissociative amnesia.

A variety of factors predict a relationship to amnesia for trauma. Interpersonal trauma, early life trauma, close personal relationship with the perpetrator, violence of the trauma, repeated trauma, sexual trauma, and level of betrayal, particularly by a childhood caregiver, all have been associated with later dissociative amnesia, although none definitively. The ACE researchers hypothesize that cumulative developmental trauma may have a generalized effect on memory systems, making substantial aspects of ordinary autobiographical memory for early life relatively unavailable for recall, not just memory for trauma.

**Dissociative Identity Disorder**

**Childhood trauma**

DID is conceptualized as a childhood onset posttraumatic developmental disorder. Every study that has examined the question of early life trauma and DID has found the highest rates of childhood adversity, primarily beginning before the age of 6, in the histories of DID individuals, compared with any other diagnostic group. In 10 studies of DID, childhood sexual abuse was found in 70% to 100% (median 83%); childhood physical abuse in 60% to 95% (median 81%); and both sexual and physical abuse in 77% to 100%, (median 94%), often by multiple perpetrators over many years. Studies of children with DID have found 95% of maltreatment reports substantiated by social services. Intensive case studies of DID adults have confirmed histories of severe, repeated childhood maltreatment based on corollary accounts, and childhood school, social service and medical records. Consistent with a lifelong, childhood onset disorder, DID has been documented in children, adolescents, adults, and in geriatric samples.

DID patients have a pattern of comorbid disorders and behaviors consistent with other severely traumatized populations. In clinical studies, 79% to 100% of DID patients met diagnostic criteria for comorbid PTSD: 83% to 96 % for comorbid depression; and 83% to 96% had a history of current or past substance abuse. In clinical studies, 92%-100% of DID pa-
patients endorsed current or past suicidal ideation; 60% to 80% reported a history of suicide attempts; 78% reported non-suicidal self-destructive behavior. Logistic regression analysis of DD patients in an inner-city clinic found that a significant relationship remained only for multiple suicide attempts and dissociation when BPD, PTSD, substance abuse, and trauma history were entered into the analysis. Across studies, DID patients spend an average of 5-12.4 years in the mental health system before correct diagnosis, receiving an average of 3-4 incorrect diagnoses. In epidemiological studies, DID individuals had significantly lower mean GAF scores compared to other psychiatric disorders, even after controlling for age and gender, and have been characterized as having a severe, chronic, persistent mental illness. DID individuals are frequently treated in more restrictive levels of care, with substantial cost to the mental health system.

Clinical presentation

Symptom patterns of DID patients differ from portrayals in the media and many psychiatric and psychology textbooks. These portrayals are characterized by florid, histrionic behavior, and repeated, dramatic state switching between highly elaborated, distinct self-states, with stable characteristics over time—like “separate people.” Factor analytic studies have generally found that DID symptoms are subtle and covert. They are characterized by overlapping and interfering states that typically manifest as inner voices or through symptoms of passive influence, not florid switching behavior—a state of multiple overlapping states. Commonly, these states are not elaborated beyond a sense of personal identity, a self-representation, a set of (state-dependent) autobiographical memories, a sense of ownership of personal experience, and a capacity to control behavior, either directly or through influencing other states. State switching may be relatively uncommon in DID, with states more typically subtly shifting, consistent with better functioning. Studies repeatedly show that clinicians must make active efforts to diagnose DID in the clinical interview, rather than expect the disorder to dramatically appear. Contrary to common belief, the elaboration of the “fascinating” external characteristics of the states, with varying names, wardrobes, hairstyles, accents, etc. is not essential to DID diagnosis or core phenomenology.

Cross-cultural studies suggest that many of these external self-state characteristics represent socio-cultural influences on DID symptoms—actually congruent with aspects of the SCM. However, the clinical presentation of all psychiatric disorders is shaped by social and cultural factors. These sociocultural factors do not invalidate DID, any more than they invalidate mood disorders or psychotic disorders. Paradoxically, psychological assessment data suggest that early life dissociation is also a protective and resilience factor that allows for preservation of capacity for attachment, psychological complexity, intellectual abilities, creativity, sense of humor, and hopefulness. When not overwhelmed by posttraumatic intrusions, DID patients show good reality testing, diminished cognitive distortions, and a hyperdeveloped capacity to observe their own psychological processes. These predict a positive response to a psychodynamically informed, insight-oriented psychotherapy. In these studies, DID patients differed significantly from BPD patients, contradicting the IM/SCM/FM.

Other studies have shown significant differences between DID and BPD, including extent and type of dissociative symptoms on the DES and SCID-D; severity and earlier onset of childhood trauma in DID; and studies showing that BPD symptoms in DID are related to severely dysregulated dissociative and PTSD symptoms, and mostly remit when the DID patient stabilizes. A subgroup of BPD patients, when administered diagnostic interviews, will meet criteria for undiagnosed DD, such as DID. Studies comparing the validity of the DID diagnosis to that of other psychiatric disorders, across the three major validity paradigms for psychiatric disorders, found that DID satisfies virtually all of the criteria for inclusion, and none for exclusion from the current DSM diagnostic system.

Childhood development and DID

Naïve views of the developmental origins of DID posit that the child’s psyche—“the personality born into the body”—is “shattered” by trauma, fragmenting the mind, and creating “separate people in one body.” A more developmentally congruent model hypothesizes that overwhelming early trauma, attachment disturbances, and lack of soothing or comfort after trauma prevent the normal development of continuity of the
young child’s sense of self across states and contexts. 63 This produces multiple senses of self, often in conflict with one another, that differentiate over developmental time. DID is more like a never-assembled psychological jigsaw puzzle, not a shattered mirror. 63 All the DID self-states constitute the mind of the person; they are not “separate people.” 72,65 Contrary to popular belief, in DID treatment, the “whole human being” is held responsible for the behavior ascribed to any self state, even if amnesia is claimed. 7

**Treatment outcome studies of DID**

Treatment outcome studies of the phasic trauma treatment model of DID 67 including recent international, prospective, longitudinal studies, have found that DID improves with appropriate treatment and that costs to the health system for DID treatment can decrease substantially as well. 2,65 In an international, 30-month, prospective, longitudinal study patients and therapists reported lower rates of hospitalization; decreased suicide attempts and self-destructive behavior; significant decreases in depression, PTSD, and dissociative symptoms; reduced substance abuse; physical pain, and general distress; and an increase in “feeling good.” Patients also evinced significantly increased engagement in relationships, work, school, or volunteer jobs. 8 A prospective study of Norwegian inpatients with a history of sexual abuse and other traumas on a specialized trauma unit, showed that, unless specifically treated, severe dissociative symptoms predicted negative outcome at 1-year follow up. 10

**Depersonalization Derealization Disorder**

DPDRD is not associated with the same controversies as DA and DID. Due to lack of professional awareness of DD, many DPDRD patients, who are often very anxious and depressed, are only conceptualized as suffering from these other disorders, as depersonalization/derealization symptoms may occur across many psychiatric diagnoses. 2,32 Lifetime prevalence of DPDRD may be about 2.5% in the general population. 2,32 Many DPDRD patients have a chronic course with severe impairment. DPDRD is strongly related to a history of childhood emotional abuse, but not to physical or sexual abuse. 5,32 Emotional abuse has been linked to adverse psychobiological outcomes, including higher dissociation scores, in non-clinical, general population samples. 38 Severely ill DPDRD patients are markedly impaired. There is no psychotropic regimen or psychotherapy that has shown consistent efficacy in alleviating DPDRD. 2,32

**Discussion**

The posttraumatic basis of dissociation/DD has been demonstrated in the vast majority of studies in clinical and non-clinical populations. 34 Dalenberg et al. 4 in a series of meta-analyses of over 1500 studies, contrasted evidence for the TM versus the IM/SCM/FM. They concluded: “…[T]hat there is strong empirical support for the hypothesis that trauma causes dissociation, and that dissociation remains related to trauma history when fantasy proneness is controlled. We find little support for the hypothesis that the dissociation–trauma relationship is due to fantasy proneness or confabulated memories of trauma.” 74 (p 550). Contrary to common beliefs, this study found that overall, average weighted effect sizes between dissociation and multiple suggestibility paradigms, accounted for 1% to 3% of the variance across suggestibility types. 4

There is an increasingly compelling alignment of genetic, neurobiological, developmental, clinical, historical, and treatment outcome data on dissociation/DD. 2 DID may be a minimum 1% of the general population; DPDRD may be as high as 2.5%. 2,32,39 By the time many DD patients are correctly diagnosed, they are demoralized and have suffered substantial secondary losses from years of unproductive treatment, hospitalizations, suicide attempts, disfiguring self-harm, disability, and careers as chronic “treatment resistant” patients. 2,32 Transdiagnostically, elevated dissociation predicts poorer clinical outcome, unless directly treated. 6,65

Treatment outcome studies of DID have shown reductions in suicidal and self-destructive behavior, as well as fewer inpatient admissions, and substantial reduced costs for treatment. 7,8,10,65 DID is a childhood onset disorder. 63 The role of dissociation in the inter-generational transmission of trauma and family violence remains a relatively unexplored area. Earlier intervention may allow better treatment of dissociative children and adolescents. 63,68

There are no studies in clinical populations to support the IM/SCM/FM. There are no treatment outcome studies to test these models. Recently, IM/SCM/FM proponents have suggested that sleep pathology is a
causative factor in dissociation and could align the TM and the IM/SCM/FM. Here, posttraumatic sleep disorders lead to dissociation, causing fantasy-proneness, memory confabulations, and, through SCM factors, a false belief in having multiple selves. They do not explore the possibility that sleep problems are symptomatic of severe DD, not causative. For example, an often refractory, multifaceted sleep disorder has been described in severely dissociative, complex trauma patients. It consists of PTSD nightmares and sleep disruptions; mood-disorder-related sleep symptoms; posttraumatic reactivity to night, bed, sleep, etc. due to nocturnal childhood sexual and physical assaults; and, in DID, nighttime interactions of self-states that interfere with sleep.

Diagnosis and treatment of dissociation/DD is a major public health issue. DD patients represent a large underserved population whose lack of recognition leads to substantial human and societal costs. Males with DD may particularly go unrecognized. The powerful relationship of dissociation, DD, and suicidal and self-destructive behavior needs to be part of efforts to lower suicide risk in general and clinical populations.

Every mental health training program should devote substantial resources to education about trauma-related disorders including dissociation/DD. Most DD research, like the recent treatment outcome studies, has been bootstrapped by dedicated researchers with minimal external funding. Funding should be directed to dissociation/DD research. Research on dissociation/DD may also make important contributions to understanding relationships of mind/brain/body through study of discrete behavioral states (DBS). DBS models may help elucidate many mind/brain/body conundrums in neuroscience, psychology, and psychiatry.

The fantasy is that DD patients do not exist. The sociocognitive problem is the cultural and professional dismissal and obliviousness to the extent and severity of the kind of trauma that generates dissociation/DD, and the ubiquity of DD patients. Failure to properly diagnose and treat DD has a very high human cost. This is the real iatrogenesis.

Disclosure/Acknowledgments: The author reports no conflicts of interest.

REFERENCES


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