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GIORNALE DI PSICOPATOLOGIA

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Assessment and instruments in psychopathology

Case reports

Dimensional psychopharmacology

Diagnosing insanity 170 years apart: Pierre Rivière and Anders Breivik

Diagnosi di follia a distanza di 170 anni: Pierre Rivière e Anders Breivik

L.S. Nilsson[1,2], A.U. Parnas[1], J. Parnas[1,2]

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Summary

Objectives

In 2011 Anders Behring Breivik, ABB, slaughtered 77 civilians in a twofold attack in Oslo and on the island of Utøya, Norway. During his trial ABB's sanity or lack thereof was fiercely contested. Two psychiatric evaluations arrived at radically different diagnoses of psychosis and personality disorder respectively. Though unrivalled in its bestiality, the case of ABB is not unique. In 1835, a French peasant Pierre Marie Rivière, PMR, in a seemingly incomprehensible act of cruelty killed his immediate family. Some contemporaries, including Esquirol, saw in PMR the traces of radical irrationality (psychosis) while others ascribed his deeds to an evil personality.

Thus a basic disagreement on the nature of rationality and madness appears to have persisted across the centuries. The aim of this paper is to clarify the sources of this diagnostic divergence and to shed some light on pressing epistemological and clinical issues related to the diagnostic process, its conceptual foundation and the question of differential diagnosis.

Methods

A 1975 book by Foucault et al. contains a manuscript by PMR detailing the background for his actions and extracts from the legal and psychiatric documents pertaining to the case. During the trial of ABB the two psychiatric evaluations were leaked to the press and made available online.

Results

In both cases the assessors had access to a very similar body of information from which the elements were selected that seemed to support their diagnostic conclusion. This selectivity led to widely different interpretations of the seemingly identical source psychopathological phenomena. The potential for a diagnostic disagreement in psychiatry has remained unresolved by the neuroscientific advances of the intervening years and, indeed, by the use of the so-called "operational" criteria.

Conclusions

The diagnostic process always involves a selection among the body of the available "objective" data. This selection process is prefigured by the diagnostician's conceptual template that structures her cognitive field and thereby renders some information relevant and excludes other as irrelevant. Moreover, the conceptual template influences the psychopathological significance of the clinical presentation. The operations of the conceptual templates or grids of prototype hierarchy are constituted by the examiner's knowledge and experience, ethical and other personal inclinations, and a host of other factors. Such cognitive constraints on the diagnostic process, already described by Jaspers, cannot be eliminated by the so-called "operational" diagnostic systems.

In the case of PMR, the major source of the diagnostic disagreement could be traced to the different levels of professionalism of the involved examiners. In the case of ABB, a nearly procrustean adherence to the ICD 10 criteria (which were not immune to different interpretations) was at the heart of the diagnostic disagreement and seemed to invite private psychological interpretations. The diagnostic disagreement in the case of ABB seems to disclose some serious because fundamental epistemological weaknesses of the ICD-10, notably an absence of a prototypical grid that is needed to structure the psychiatrist's cognitive field and an impossibility of adequate description and definition of the psychopathological phenomena (symptoms and signs) through the so-called "operational criteria", i.e. brief, simple, lay language statements. Defining the diagnostic classes by a specific number of seemingly mutually independent features, and without any emphasis on the phenomenological typicality or structure of both the diagnostic class and its constituents, is likely to entail diagnostic distortions. Finally, it is suggested that in terms of diagnosis, the notion of the schizophrenia spectrum appears as being highly relevant in both cases.

Key words

Breivik • Rivière • Psychosis • Rationality • Nosology • Diagnosis

Introduction

In 2011 Anders Behring Breivik (ABB) murdered 77 civilians in a twofold attack on downtown Oslo and the island of Utøya, Norway. During his trial there emerged a fierce debate among mental health professionals and the general public on the issue of his potential insanity. Two diagnostic evaluations (according to the ICD-10 criteria), performed by independent psychiatric teams, arrived at radically different conclusions. The first found ABB to suffer from paranoid schizophrenia whereas the second diag-

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nosed him with narcissistic personality disorder with antisocial traits. On the basis of the second evaluation, ABB was sentenced to 21 years in preventive custody with a minimum time of 10 years. The forensic details and the debate surrounding the Breivik case were commented upon in World Psychiatry [1].

A somewhat similar, though much less spectacular incident happened in France in 1835. A young peasant, Pierre Marie Rivière (PMR), murdered his mother, sister and brother. He was examined by a local physician and was first considered sane. However, a second psychiatric evaluation and additional review of all documents pertaining to the case, performed by the renowned Parisian alienists Esquirol and Leuret, diagnosed PMR with psychosis. PMR was therefore not condemned to death. However, some years later he committed suicide in prison.

We intend to present and compare both cases, juxtaposing the psychopathological considerations involved in assigning the respective diagnostic sets. For that purpose, we will use the forensic-psychiatric information concerning PMR and ABB that is publicly available (see below). This presentation is to serve as a basis of a reflection on pressing epistemological and clinical concerns related to the nature of the diagnostic system, the diagnostic process and differential diagnosis [2]. The story of PMR, which took place at the birth of modern psychiatric nosology, will highlight certain recurrent, and therefore general problems confronting the process of psychiatric diagnosis. We will then explicitly articulate the conceptual and clinical issues implicit in the a-theoretical polythetic "operational-criteria" based system, as compared to its predecessor (e.g. ICD-8), namely a prototypical classification whose constituent classes are organized around the narrative descriptions of category-characteristic prototypes and associated phenomenological and theoretical reflections.

Information sources

The 1975 book "I, Pierre Rivère, having slaughtered my mother, my sister, and my brother … A case of parricide in the 19th century" [3] edited by Michel Foucault et al. contains a manuscript by PMR detailing the background for his actions, extracts from the legal documents, and the psychiatric evaluations of PMR.

During the trial of ABB, the two successive psychiatric evaluations were leaked to the press and made available online [4].

The case of Pierre Marie Rivière

Childhood

PMR was born in 1814 in a small village in Normandy, France, as the oldest of five siblings. His peasant parents were widely known to be living in a disharmonious relationship. The court witnesses testified that the mother exposed her husband to abuse and violence. PMR was fond of his father but considered his mother a mean and wicked woman, who would drive her husband "… to such despair that he was sometimes tempted to commit suicide" [3, p. 24]. PMR terminated his schooling at the age of 12. The local priest found him to be intelligent, curious, and interested in religion and science. He was ambitious and strived to rise above his status. However, PMR "lacked the tact" required to interact with other people.

Around the age of 8 PMR changed. He became introverted, increasingly isolated, cruel to other children and animals, and displayed bizarre behavior. He desperately tried to "… live in society, but I did not have tact enough to do that, I could not find the words to say, and I could not appear sociable with the young people of my own age" [3, p. 103]. "Later my ideas changed and I thought I should be as other men. Nevertheless I displayed peculiarities. My schoolmates noticed this and laughed at me (…) Above all I had a horror of incest which caused me to shun approaching the women of my family. When I thought I had come too close to them, I made signs with my hand as if to repair the harm I believed I had done" [3, p. 101-2]. Several witnesses emphasized his cruelty. He tortured and crucified frogs and birds and he even invented a new torturing technique, which he named in his memoirs as "enceepharating" [3, p. 104]; it consisted of transfixing the animal to a tree with three sharp nails through the abdomen.

The crime

PMR grew increasingly preoccupied with his father's situation and the suffering inflicted on him by the mother and he began contemplating how best to protect and save him. One day, at a church ceremony, he witnessed several people begin to weep when his father intoned a psalm. At that very moment he decided to kill his mother, sister and little brother. The sister had to die because PMR considered her to be an accomplice of his mother. His little brother also had to die, but for different reasons: partly because of his love for these two women, partly because the killing of the brother would make his father abhor PMR so much "that he will rejoice in my death" [3, p. 106]. PMR described in his memoirs how thoroughly he contemplated and planned his crime, e.g., with details concerning timing and the clothes he was to wear. He minutely described the murders. The police report quotes the neighbours to have heard PMR say just before fleeing the house: "I have just delivered my father from all his tribulations. I know that they will put me to death, but no matter" [3, p. 39]. PMR fled into the woods where he roamed for days before being apprehended and questioned by the police.

Psychiatric evaluations of PMR

In the prison, PMR spent 11 days completing his manuscript with the famous opening lines: "I, Pierre Rivière, having slaughtered my mother, my sister, and my brother …" [3, p. 54]. Several witnesses from the village and PMR's own family were interviewed during the investigation. Some gave detailed accounts of PMR's bizarre behaviour and described his fear of women, his tendency to talk to himself while alone, and his complete isolation from his peers. Others, however, mainly emphasized his cruelty, his preference for solitude and they expressed doubts about his intelligence.

During the trial, the prosecutor highlighted the precocity of PMR's cruel character, his intelligence, curiosity in school, and his ability to meticulously plan his acts, while the jury suspected that his cognitive abilities might have allowed him to simulate madness. His manuscript was considered proof of both his intellectual abilities and an insight into the immorality of the crime.

Several physicians and psychiatrists examined PMR with different conclusions on his mental state. The doctor who observed PMR during his incarceration had not noticed any signs of insanity or disturbed intelligence. A general practitioner without any special knowledge of psychiatry, Dr. Bouchard, was tasked with drafting a psychiatric evaluation immediately after PMR's arrest. He did not observe any signs of mental illness - idiocy, mania or dementia - and he emphasized PMR's intact cognitive functioning: "Pierre Rivière is not a monomaniac, because he does not harbor delusions on one and only one subject; he is not a maniac, because he is not in a habitual state of agitation; he is not an idiot, because he has written a wholly sane memoir …" [3, p. 141]. Dr. Bouchard omitted in his report any reference to the disposition to mental illness on the maternal side of the family, the unequivocally established history of personality change, change of behavior and its grossly bizarre elements, as well as PMR's fearful ideas concerning incest. Instead, he emphasized that PMR never suffered from illnesses or injuries that might have affected his brain functioning. Dr. Bouchard pointed out the shocking tranquility with which PMR spoke of his crime and concluded that: "Nothing in his answers indicates any derangement of the mental faculties" [3, p. 123]. Rather, he considered PMR to be of a "melancholic character" with a preference for solitude and cruelty. This account resonated with the prosecutor's indictment: "… from his childhood [PMR] gave signs of a savage character which to this day has led him to avoid young persons of his age and seek solitude" [3, p. 49]. In other words, PMR did not display the erratic behavior of the insane but rather proved himself "(…) taciturn and reflective, with an ardent, cruel, and violent imagination" [3, p. 49].

A psychiatrist in charge of the psychiatric asylum in Caen, Dr. Vastel, was also asked to examine PMR and give his own medical opinion. He pointed to a hereditary element of madness on the maternal side of PMR's family. He found PMR to have suffered from insanity since childhood. He drew attention to the fact that PMR explained his fear of incest with a belief that a fluid with some mysterious incestuous properties was being emitted from his own body. Moreover, Dr. Vastel stressed the bizarre quality of PMR's asocial behavior and, finally, he emphasized that PMR's reflections or motivations behind his crime (a belief that the triple-murder would ultimately pave the way for his father's liberation and future happiness) were a mark of insanity in their own right. In his view PMR was a mad and dangerous man.

Finally, a group of Parisian alienists, including the renowned Esquirol and Leuret, was asked to give their expert opinion about PMR's mental state based upon a review of all files pertaining to the case (police records, medical documents, and PMR's manuscript). They firmly concluded that PMR was indeed insane, had exhibited signs of madness since his childhood, and that his deluded mind was the reason behind the crime.

The jury, however, found PMR guilty and sentenced him to death. Yet, because of a persisting uncertainty among the judges, King Louis Philippe was asked to intervene. Following the advice of his minister of justice the king granted PMR a partial pardon because seemingly the crime per se – as one newspaper put it – "bore every sign of insanity" [3, p. 171]. PMR's death sentence was therefore converted to life imprisonment. Some years later, PMR committed suicide.

The case of Anders Behring Breivik

The story

ABB was born in 1979 in Oslo, Norway and following the divorce of his parents he grew up with his mother and half-sister. At the age of 4 he was examined by the Child Psychiatric Service. A recommendation to place him in foster care never materialized, however. His development over the next few years seems to have been fairly inconspicuous. However, as a teenager he was apprehended for petty crimes and he dropped out of high school in his third year. He then started a string of companies, the last of which sold fake academic diplomas. This was shut down in 2006 due to legal concerns and a few months later he moved back in with his mother. Over the next years he grew increasingly isolated and devoted his time to online gaming, preparing his terror act and writing the 1518 pages manifesto "2083 – A European Declaration of Independence", which in three books detailed

his motivation for the coming attacks. Book 1 offered a subjective history of Europe, focusing on the threat allegedly posed by Islam, book 2 addressed the current situation, and book 3 encouraged the reader to partake in the outlined ideological struggle. Whereas large parts of the first two books were directly lifted from a range of far-right websites, ABB seemed to have been the main author of the third.

July 22nd, 2011 ABB detonated a car bomb in the downtown government quarter in Oslo, killing eight people and severely injuring others. Two hours later, he travelled from the bombsite to the small island of Utøya, where a summercamp of the Norwegian social-democratic youth organization took place. He arrived dressed as a police officer and immediately started firing at the hundreds of persons gathered on the island, killing, execution-style, 69 persons, mainly children and adolescents, while injuring many others. Survivors reported that he was laughing and shouting while shooting. After 50 minutes, he called the police saying: "Yes, hello, my name is Commander Anders Behring Breivik from the Norwegian anti-communist resistance movement. I'm on Utøya for the moment. I want to give myself up" [1]. Finally, ABB was apprehended by the police and subjected to a forensic psychiatric assessment.

The first psychiatric assessment

Two court appointed psychiatrists conducted 13 interviews of a total duration of 36 hours with ABB, in addition interviewing his mother and hearing or viewing all police interrogations. They combined unstructured with structured diagnostic interviews. On November 29th 2011 they submitted their report, diagnosing ABB with paranoid schizophrenia. ABB was considered to be psychotic both at the time of the assessment and at the time of his crime. Melle [1] provides an excellent summary of the assessment:

"This conclusion was based on central contents of Breivik's thought system. He told (...) that he had "precedence as the ideological leader for the Knights Templars organization, with the mandate of being both a military order, a martyr organization, a military tribunal, judge, jury and executioner". He thought he was a pioneer in a European civil war, and compared his situation to that of Tsar Nicolas of Russia and Queen Isabella of Spain. He believed that it was likely (with somewhat varying degrees of likelihood) that he could be the new regent in Norway following a coup d'état. He said he decided who should live and who should die in Norway. This responsibility was felt as real, but also a heavy burden. He believed that a considerable proportion of the Norwegian population (several hundred thousands) supported his deeds. If he became the new regent, he would take the name Sigurd the Crusader the Second (Sigurd the Crusader was a Norwegian medieval king who reclaimed parts of Portugal from Muslim rule). (:::) He thought he would be given the responsibility for deporting several hundred thousands of Muslims to North Africa. He believed there was an ongoing ethnic cleansing in Norway and feared for his life. He thought the events he was a part of could start a nuclear third world war. He worked with solutions to improve the Norwegian ethnic genetic pool, make illnesses extinct and reduce the divorce rate. He thought about reservations for indigenous Norwegians, DNA testing and factories for mass deliveries of babies. He believed that the house of Glucksburg (current Norwegian royal house) would be removed through revolution in 2020. As an alternative to recruiting a new regent from the leadership of the Knights Templars, one could make DNA tests of the remains of King Olav the Saint (the Viking King who introduced Christianity to Norway) and then choose the one with best genetic likeness to be the new king.

The psychiatrists saw these as grandiose delusions with bizarre and paranoid qualities that went far beyond conspiracy notions about an Islamist take-over of Europe. They thus did not consider him psychotic by mistaking his extremist, racist, right-wing views as delusional, but because they thought he had grandiose delusions regarding his own role in this extremist universe. While his political opinions unfortunately are shared by others, he stood alone in his claims of an exalted role in the alleged Knights Templars organization, or even in the claims of this organization's existence. In addition, Breivik claimed he had exceptional personal abilities, for instance knowing what other people – including his evaluators – thought, without fully explaining them how.

The two psychiatrists perceived his language as stilted and technical, using common words in new contexts mixed with unusual words, which he said he had made himself and that the psychiatrists perceived as neologisms. There were otherwise no signs of grossly disorganized speech or actions. He usually displayed restricted, but sometimes also inappropriate affect when talking about his killings, which he called "the executions of traitors". He got animated when talking about his shooting rampage and about his Manifesto. The psychiatrists saw this as an example of affective flattening with incidents of incongruent affect. There were no outward signs of depression, mania, auditory hallucinations or ideas of reference, influence phenomena or ideas of thought insertion".

In dealing with ABB's manifesto, the experts stated their intention to abstain from passing judgment on his political convictions. However, they were puzzled by his explicit intention with the document, namely to "*save Europe from multiculturalism and an Islamic take-over* (original italics)" [5, p. 57], because this seemed to clash with its "banal

and to some extent downright infantile mode of expression" [5, p. 57]. Since ABB made the impression of an intelligent man, they struggled to understand what might motivate such incongruency. Thus they speculated that it might be due to him having lost "the overall cognitive and intellectual functions [that] one would expect him to employ in order to assess the outside world's experience and understanding of the product" [5, p. 57]. Accordingly they found the manifesto to be "almost pathetically egocentric" [5, p. 58] in its detailed descriptions of meaningless trivialities of ABB's daily life, and argued that this was a function of his grandiose ideas: "(…) I will always know that I am perhaps the biggest champion of cultural conservatism, Europe has ever witnessed since 1950" [5, p.61]. This was also, they argued, what drove ABB to include a section offering the reader farming advice, which to the experts seemed "very weird or bizarre in the context" [5, p. 64].

The second evaluation

However, a chorus of more or less informed opinions exploded when the diagnostic conclusion was leaked to the press and became available online. Laymen, psychiatrists, and other professionals immediately questioned the diagnosis. ABB himself felt offended and explicitly wanted to be viewed as a sane person engaged in a mortal ideological struggle. The public debate was quite vocal, at times even virulent, and spread to the rest of Scandinavia. Some people feared that a psychotic ABB would avoid punishment and soon be walking the streets. Moreover, some, among the politically correct, preferred to see ABB as a sane extreme right-wing terrorist, thus testifying to the fact that terror is not an exclusive attribute of radical islamism.

In response to all that turmoil, the court appointed a second pair of psychiatrists in January 2012 for a re-assessment. This was carried out six months after the first. By that time, ABB had for several months undergone frequent consultations with the psychiatric treatment team in the prison. No longer in isolation, he also had access to the first psychiatric report and to the details of his mental condition as debated in the media.

The main part of the new evaluation was based on the same instruments as the first. However, additionally a 3 week in-patient observation in the prison by trained psychiatric personnel was carried out. The psychiatrists submitted their report in April 2012. It firmly rebutted the previous diagnostic verdict and concluded that ABB was not psychotic but suffered from a narcissistic personality disorder with antisocial traits. On August 24th 2012 the court judged ABB to be compos mentis and sentenced him to 21 years of confinement with a possibility of prolongation.

The second evaluation could essentially be seen as an attempt to systematically deconstruct its predecessor's main conclusive sections. We will therefore look at the most significant chunks of this evaluation.

1. Past information

Approximately 5 years prior to the attack, ABB moved back in with his mother (highly unusual in Scandinavia), and withdrew from social interaction. In the first evaluation ABB's mother is interviewed in an effort to shed light on this move and the behavioral changes that ensued. The second evaluation, on the other hand, relied solely on information from the police interrogations. However, the contents of the family interviews by psychiatrists in the first assessment and the police interrogations used in the re-assessment, differ significantly.

In the first report ABB's mother explained how a rather sinister transformation set in around 2006 and became dramatically accentuated in 2010. She found her son "all weird" [5, p. 79]. Either he would refuse to leave his room or he would sit awkwardly close to her. She found it increasingly difficult to follow his flow of speech as he brought up the names of past Danish kings, warlords, and "all kinds of strange things" [5, p. 81]. She felt unsafe and explicitly feared that he might be going insane.

On the other hand, the description she gave to the police and thus the one used in the second evaluation is very different. Here, she expressed her disbelief that her son might be involved in such a hideous crime and stressed how reasonable, mature, and kind he always was. She admitted that something about him had changed but the bizarre air of this alteration (elicited by the first team of psychiatrists) was absent here, and none of the previous information was taken up in the second assessment. Instead, it was stated in the second evaluation that ABB had changed slightly in the winter of 2011 and started working out a lot. The mother felt as if "he was a different person" [6, p. 87], but the nature of this transformation was not developed. Instead, it was explained with a reference to ABB's use of anabolic steroids: "She thought it had to do with "all the drugs he was taking" [6, p. 87].

2. The question of delusionality

The second evaluation also rebutted their predecessors' claim to have identified a number of delusions. This rebuttal concerns, for instance, an entry in the record of ABB's general practitioner in the spring of 2011: ABB expressed a worry that he might have been infected with his mother's sinusitis even though he had made a habit of wearing a mask indoors. During the first evaluation, ABB's mother explained that he ordered her not to sneeze, refused coming into the kitchen, and took his meals in his own room. He began walking around with his hands covering his face and for some time he

did indeed wear a mask. The first evaluation categorized this behavior as being expressive of delusional ideation. The second psychiatric team refuted that assessment. Not having addressed the issue directly with ABB, they based their appraisal on a brief psychiatric evaluation carried out in prison shortly after the first report was finalized and made public. ABB felt insulted upon learning his diagnosis. He declared that he would take the opportunity to modify some of his earlier statements in order to be judged compos mentis. Thus, with respect to the fear of infection, he now pointed out that he only wore the mask because he was eager to be fit for a shooting competition and denied having been fearful of getting infected in other contexts. On these grounds, the second team of experts decided to: "interpret the story of the mask differently, namely as exaggerated caution/hypochondria but with no failure of reality testing" [6, p. 219]. They concluded that nothing suggested that ABB should have harbored somatic delusions at any point.

Concerning ABB's belief system revolving around the Muslim take-over, left-wing complacency, preservation of a pure Norwegian genetic pool, and Knights Templars (an organization which does not exist), the second evaluation agreed with the first that ABB harbored pathological self-aggrandizement. However, by the time of the second assessment ABB downplayed the importance of the Knights Templars and pictured himself as a "foot-soldier", performing his duties and explained that he earlier had exaggerated his own role. The second evaluation stated that ABB had "ideas of heightened self-worth, power and knowledge that may be reminiscent of what is observed in delusional disorders. Not least the ideas concerning the Knights Templars appear peculiar. He has, however, rationalized this and explained that it is a *willed idea* (our italics)" [6, p. 225].

3) The negative symptomatology

ABB's practical involvement in the world was very limited from 2006 onwards. In the first evaluation his mother described how he inverted his circadian rhythm and spent most of his time in his own room. This was viewed in the first evaluation as being emblematic of developing negative symptomatology. The second evaluation, however, emphasized the rationality behind the withdrawal, namely ABB's wish to dedicate himself exclusively to his ideological project, pointing to "a willed and calculated action" [6, p. 223]. Furthermore attention is called to the apparent unlikelihood of a schizophrenia patient paying rent while living with his mother: "In a clinical setting it is not seldom seen that schizophrenic patients move in with their parents in the early stages of their illness *but usually they do not pay for it*" [6, p. 223] (our italics).

Both evaluations found that ABB exhibited blunted affect (also visible during the TV coverage of his trial) but differed entirely in evaluating its significance. The first report considered blunted (and occasionally incongruous) affect as clearly reflective of the negative domain of the clinical picture of schizophrenia, whereas the second assessment saw it "a token of failure of empathy"[6,p.222] and concluded that his "emotional flattening is not judged to be of the type that is seen in severe mental disorders but is understood to be expressive of pathological personality features" [6, p. 263].

4) The formal thought disorder (disorder of speech)

The first evaluation emphasized the presence of formal thought disorder severe enough to count as a diagnostic criterion for schizophrenia. They described loosening of associations, perseveration, and a tendency to employ mathematical terms where they were utterly out of place. Finally, they pointed out a significant number of self-created expressions such as "suicidal-humanist" and "knight-justiciar-grandmaster", which they qualified as neologisms. The second evaluation conceded that ABB's language usage was somewhat peculiar. Thus, the suicide risk assessments carried out in the first period of his incarceration mention, for instance, that ABB described his joie de vivre as alternating between 10-30% with apathy occurring at 0%. But rather than seeing those statements as indicative of psychopathology, the second assessment concluded that they were a rational and creative measure. Explicitly invoking ABB's own reference to an "effective means of communication" [6, p. 237], they stressed that it should not be viewed as "a sign of aberration" [6, p. 237]. Similarly the second evaluation acknowledged that ABB used a significant number of homemade words but rejected that this should be tantamount to formal thought disorder. Instead it is argued that since a word like "anarcho-jihadist" was made up of two existing words, it could not qualify for a neologism at all. The experts reasoned that the emergence of such words is an integral part of any dynamic language while neologisms should be understood as word-formations "wholly unknown and unintelligible to others" [6, p. 262]. This, then, allowed them to conclude that no schizophrenic formal thought disorder was detectable in the case of ABB.

5) The manifesto

The second evaluation offered a reasonably lengthy resume of the manifesto thus mapping out much of the thought system described by Melle. It also mentioned a reading by the Norwegian Police Security Service, pointing out that the document remained difficult to access in spite of its many chapters, because it was characterized by many repetitions. The experts conceded that they had no special authority on political or ideological matters but maintained that in order for them to fulfill their terms of reference they needed to address these issues nonethe-

less. They then concluded that aberrant and unacceptable as ABB's ideological aims may be, they were shared by a number of political subcultures and thusly not indicative of psychotic thought processes. Furthermore they stipulated that the sheer amount of research and work put into writing the manifesto by ABB was incompatible with (schizophrenic) withdrawal and psychotically conditioned loss of functioning.

Discussion

Similarities

The stories of PMR and ABB bear a significant resemblance, corresponding pointwise to each other with respect to the overall nature of psychopathology, the type of crime, and the motivations of those crimes by specific sets of beliefs. Both perpetrators found it worthwhile to produce a manifesto. In both cases, the ability to write a manifesto, and other indications of intact intelligence, were considered by some as being incompatible with the notion of psychosis. In both situations, a descriptive psychodiagnostic approach was employed, resulting in a diagnostic disagreement, vacillating between personality disorder and psychosis. Thus, despite the spectacular scientific, and especially neuroscientific, advances of the 170 years separating these events, on both occasions the diagnostic decisions were unanchored in any extra-clinical/neurobiological findings but relied exclusively on the interpretations of clinical descriptive data.

In both cases, the sets of assessors had access to a very similar, if not identical, body of information, from which they selected the elements that seemed to point to and support their diagnostic verdicts.

The reading template

A co-worker of Foucault, Philippe Riot [7], analyzed how, in the case of PMR, information was being sorted in the process of addressing the question of PMR's potential (in)-sanity. Foucault and Riot introduce here a notion of a "grille de lecture" or "reading template" (or, more broadly, "comprehension template"), a template, "which operates by a selection among the whole body of facts reported by Rivière and the witnesses and [which] sets up a coding system for their interpretation" [7, p. 235]. The reading template, so to say, *prefigures* the selection process, i.e. what, in fact, is being "read" at all, and what is seen as relevant. The examiner's conceptual sophistication, his professional knowledge, ethical inclinations, his cultural-social context, and a host of other, often tacit or hidden motivations and assumptions constitute a given template. The notion of a template is an instance of a larger question, namely the very nature of the epistemic or cognitive subject-world relation. What is relevant and what counts as a "fact" or "information" among the chaotic myriads of seemingly unconnected data, initially confronting us in any epistemic situation? Cognitive science talks here of the so-called "frame problem", i.e. "the issue of how to decide what is relevant, indeed what is even the relevant overall context within which to approach a given problem" [8, p. 356]. Phenomenology and cognitive science operate with the notions of prototype-gestalt and typification. Perceiving something is to perceive it *as a something*, i.e., as a token or instance of a certain type. This is intrinsic to all cognition and hence to the psychiatric diagnostic process as well. We always apprehend a clinical situation through a conceptual grid or template that imposes a provisional hierarchical matrix of relevance and signification on the single elements of the cognitive field. In other words, the epistemic act always activates a guiding prototype. Recent authoritative reviews of cognitive and theoretical research on mechanisms of concept formation, use, and understanding, suggest that concepts (thus including diagnostic and other psychopathological concepts) are not constituted by a list of criteria (which is called "the classical view") but are rather organized around prototypes [9]: a "(…) theory of concepts must be primarily prototype-based (…), within a broader knowledge representation scheme in which the concept is positioned both within a hierarchy and within a theoretical framework(s) appropriate to that domain" [10].

The creation of contemporary diagnostic systems such as DSM-III-5 and ICD-10 was, in fact, an epistemological regression. It was essentially motivated by a wish (theoretically and empirically uninformed and already outdated during the creation of DSM-III [for details see Parnas and Bovet 2014]) [11] to eliminate the influence of prototypical templates and to replace them with "objective" criteria ("objective" templates), i.e. basing the psychiatric diagnosis primarily on *a specific number of certain symptoms and signs* (see Nordgaard et al., 2013; Parnas et al., 2013) [8 12]. Those symptoms and signs were erroneously believed to be unproblematically definable through brief, lay language descriptions, independently of other symptoms and independently of any contextual relations (see Parnas and Bovet, 2014) [11].

The templates involved in the case of Rivière

In the PMR case, the role of different "reading templates" is easy to detect in the professional backgrounds of the involved parties. The "sanity"-party (the police, lawyers and Dr. Bouchard, all non-psychiatrists) did not ascribe any significant value to the historical information and failed to detect delusions as well as a flagrant irrationality of the motivation behind the triple murder. PMR's apparently high intelligence was interpreted as counting against

the possibility of psychosis. Their assessment pictured a malicious and cruel personality. The "insanity" party, on the other hand, was composed of psychiatrists. Among them was Esquirol, the ultimate authority on the issue of madness and the author of the first modern psychiatric textbook [13], and the man who developed the concept of "monomania", a precursor term for "delusion". Moreover, the French alienists were able to express their opinion without any distracting worries about political correctness, pressure from the public or the media. They took an inclusive or global view, thus also emphasizing the general sense of irrationality, not exhausted by isolated "monomaniac" statements. They concluded: "1) That Pierre Rivière consistently showed signs of madness since the age of four; 2) That his mental disorder persisted, though to a less intense degree, after the homicides he committed; 3) That the homicides are due solely and exclusively to delusion" [3, p. 165]. Furthermore they pointed out how some "mental defectives" [3, p. 165] experienced a temporary amelioration of their symptoms after their crime. What is remarkable here is the grasping of a gestalt of the entire story in its evolutive detail and the arrival at a portrait of an irrational, increasingly isolated person.

Templates in the case of ABB

The case of ABB is much more convoluted to assess. Independently of any further clinical or conceptual concern, it seems almost beyond belief that the two sets of psychiatrists could arrive at so different diagnoses. There were no known professional differences between the assessors. Both teams framed their diagnostic considerations in the terms of the ICD 10 (officially in use in Norway), serving as a part of their "reading template". Both teams had access to similar information. One potential and plausible source of difference is the time lag of approximately 6 months separating the two assessments. Yet the possibility of an amelioration of ABB's mental condition during his confinement (with regular psychiatric consultations during that time) was rejected in the second assessment. Another likely possibility, that ABB went to great lengths in order to dissimulate his condition (retracting, modifying or explaining away his initial statements) was dismissed by the second assessment with references to the lengthy interviews and the around the clock observation of his prison *behavior* during a period of 3 weeks, an observation that failed to detect hallucinatory attitudes, catatonic behavior or other bizarre features. A third factor, on which we only can speculate in the absence of any explicit information, is a potential effect of the court's unprecedented decision to order a second evaluation, even though the first one was duly approved by the Norwegian Psychiatric Forensic Council. The court's decision came in response to a *vox populi*, demanding, what was believed to be proper justice, i.e. an ordinary punishment rather than a psychiatric sanction. Norway's Prime Minister channeled that popular atmosphere by publicly stating shortly before the beginning of the trial that the country would be best served with a verdict of ordinary punishment. In other words, the very fact of ordering a second assessment might have carried with it an implicit message to find ABB non-psychotic and accountable for his horrific crimes.

The structure and content of both assessments correspond to the single ICD-10 criteria, even approaching a procrustrean level. As an example, the first evaluation saw ABB's delusions as being "bizarre". We agree with the presence of the element of "bizzareness" as this term is understood in phenomenological psychiatry [14]. However, the definition of "bizzareness" in ICD-10 and DSM-IV seems to include a feature of (physical) impossibility, which does not appear to be fulfilled by any of ABB's statements. The structure of the second psychiatric report resembles a point-by-point debunking of the first report, rather than providing an independent, de novo argument for the diagnosis of personality disorder. For example, one may wonder how compatible the notion of a narcissistic personality is with the absence of interpersonal relations (social isolation)? Would anonymous online gaming be a satisfactory substitute for personal relations in meeting the criterion of "desire for admiration", *constitutive* of the non-psychotic narcissism [15 16]? Is ABB's apparent solipsistic grandiosity of the narcissistic kind?

The "diagnostic criteria" of the ICD-10 (i.e., the symptoms and signs) are contrary to popular belief not "operational" in any epistemological or scientific sense. They are just brief common sense descriptions phrased in an ordinary non-technical lay language at "the lowest order of inference" [11]. This is, of course, a very serious deficiency of the polythetic system, whose categories are based on "symptom counting" [17]. This is amply illustrated by the disagreement on ABB's mental state. The ICD-10 "criteria", simplified into a-contextual primitives, fail to disambiguate the diagnostic questions. Even the relatively unambiguous definitions of behavioral "signs" (e.g. blunted affect) did not prevent the psychiatrists from engaging in psychological interpretations (see above: the negative symptoms and formal thought disorder).

The most significant problem confronting the ICD 10 approach is that psychiatric symptoms and signs are, in fact, *not* atomic, mutually independent entities, devoid of meaning, and ready to enter a diagnostic algorithm through their sheer sufficient number [8 18 19]. Rather, major psychiatric disorders and their component features (symptoms and signs) manifest (and were originally constituted by) their gestaltic salience [11]. The discussion of ABB's potential psychosis serves as an excellent illustration of the issue of gestalt. Thus, the second psychiatric evaluation, splitting up the psychopathological picture

into seemingly atomic, self-sufficient components, and addressing these one at a time and independently of each other, arrived at a gradual normalization of what at the first reading appeared as a sheer case of madness. However, ABB's isolation, fear of infection, bizarre home behavior, plans for genetic purification of Norway, membership of Knight Templars, and, most importantly, his logic behind murdering scores of social-democratic youngsters in order to prevent them from growing into potential future pro-islamic politicians, hardly appear, in our eyes, as mutually independent ideas, propositions, or contingent episodes of unrelated behaviors. Rather, they seem to operate as *interdependent aspects* of a *radical irrationality* or deficient "we"-perspective, characteristic of the psychotic disorders [20]. In fact, ABB's plan behind the crime closely resembles that of PMR: both plans can perhaps withstand a critical examination from the perspective of formal logic. At the same time, however, those plans violate "the logic of the world" [21], i.e., our pre-reflective, ante-predicative, and very basic attunement to the shared world, a "vital contact with reality" [22] or "common sense" [23]. In both crimes, we may therefore talk about "autistic activity" [22] or of "crazy action" ("Unsinnige Handlung") [24], a characteristic phenomenological feature of the schizophrenia spectrum disorders. As a matter of fact King Louis Philippe's minister of justice, a layman, recommended commuting PMR's sentence precisely because the parricide, in its motivation and execution, appeared to him as insane.

Conclusions

Prototypical considerations

Recently, we have witnessed a broad disappointment with the contemporary polythetic operational diagnostic systems, which have not only failed to translate into advances of etiological knowledge but also resulted in severe restrictions of clinical utility of psychiatric diagnosis [25 26 27 28 29 30]. These problems comprise a marked ignorance of descriptive psychopathology [26], high levels of co-morbidity (defying conceptual understanding), arbitrary diagnostic thresholds, "epidemics" of fashion diagnoses (e.g., the autistic spectrum, ADHD, "Borderline" etc.), and nearly insurmountable problems of differential diagnosis[2]. This latter issue is closely linked to the clinicians' lack of a prototypically organized grid that needs to be deployed in any diagnostic situation. This problem cannot be alleviated by a manual of differential diagnosis that consists exclusively of a multitude of computer-ready binary decision trees, each one starting from a different complaint [31]. These negative consequences and the stagnation of clinical psychiatry do not only follow from the complexity of the brain and human behavior or from fallible human implementation of the polythetic-operational ideas. Rather, the problems stem directly from the erroneous epistemological foundations of the entire operational project [11]. Defining diagnostic classes without any conceptual considerations of their phenomenological typicality and organizing structures is bound to create serious diagnostic confusions [2 20 32]. As an example, the DSM-IV diagnostic algorithm for "major depression" (where the composite criteria, e.g., psychomotor retardation/agitation, are split into the single symptoms) results in 1497 possible symptomatic combinations [33]. If the diagnosis "depression" is solely based on "symptom counting" and unaccompanied by a theoretical grasp of what we mean by the concept of depression and its corresponding prototypical-clinical instantiation (i.e. conceptual/construct validity), then the diagnostic category becomes a purely nominalistic label, devoid of meaning and applicable to a variety of disparate mental disorders.

Rivière and Breivik: the same prototype?

From our external point of view, nothing in the publicly accessible material regarding either PMR or ABB seems to be in contradiction with the diagnostic notion of a schizophrenia spectrum disorder. Schizophrenia is not only a mixture of positive and negative symptoms (defined at a very high severity level) with clear borders, as the DSM-5 and ICD-10 would have us believe. In empirical reality, schizophrenia is a certain prototypical gestalt that extends to milder, less symptomatic conditions, jointly designated as the schizophrenia spectrum disorders (SSD). It is not uncommon that an individual patient may occupy different of the SSD sub-categories over time [34]. The SSD is perhaps the most heavily research-validated psychiatric category [35] and it comprises in the ICD-10: schizophrenia, other non-affective psychosis, schizotypal disorder and perhaps paranoid personality disorder. The generative core of this gestalt comprises a dislocation from the shared, social world, inadequate grasp of shared meanings, fundamental disorders of self-experience and rationality, with an emergence of variously articulated, private ontological frameworks. These central features were subsumed by Bleuler, Minkowski, and Blankenburg, under the term of "autism" [36 37].

Both perpetrators seemed to manifest a psychopathological gestalt marked by interpersonal isolation and solitude, inadequate or bizarre interpersonal behaviors, indices of formal thought disorder, or more broadly, forms of radical irrationality, psychosis-near symptoms and frank delusions. The concepts of prototype and spectrum allow here for an intrinsic dimensionality of the clinical manifestation, with a possibility of clinically familiar oscillations between frankly psychotic and subpsychotic mental states.

Conflict of interests
None.

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Resting energy expenditure in a cohort of female patients with bipolar disorder: indirect calorimetry *vs* Harris-Benedict, Mifflin-St. Jeor, LARN Equations

Dispendio energetico a riposo in un campione di pazienti di genere femminile con disturbo bipolare: calorimetria indiretta vs equazioni Harris-Benedict, Mifflin-St. Jeor, LARN

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Summary

Objectives
To compare predictive formulae commonly used to calculate resting energy expenditure (REE) with the indirect calorimetry (IC) in a sample of female outpatients with bipolar I disorder, stabilised with long-term psychopharmacological treatment.

Methods
Seventeen female patients with bipolar I disorder were evaluated with an IC instrument (VO2000). IC values were compared with the Harris-Benedict, Mifflin-St. Jeor and LARN equation methods.

Results
The measured REE was not significantly correlated with the three equations. The mean differences between REE values estimated with Harris-Benedict, Mifflin-St. Jeor and LARN equations, and the value measured with IC was significantly different from zero. Moreover, a significant difference was found between the mean REE values measured with the IC and the mean values estimated with the three equations.

Conclusions
Equations commonly utilised for the assessment of REE are not alternatives to IC in female patients treated for bipolar I disorder.

Key words

Bipolar disorder • Calorimetry • Energy expenditure • Equation methods

Introduction

Weight gain, glucose intolerance, diabetes mellitus, hypercholesterolaemia and hypertriglyceridaemia are unwanted effects that can occur during psychopharmacological treatment of bipolar disorders [1 2]. The mechanism underlying weight gain that frequently occurs with the psychopharmacological treatment of bipolar disorders is still under debate. It has been hypothesised, for example, that atypical antipsychotics may trigger weight gain not only for the combined affinity for 5-HT2c serotonin and H1 histamine receptors [3], but also for the induction of a positive energy balance [4]. The management of excessive weight gain and obesity in patients treated with atypical antipsychotics is currently emphasized in the literature, and includes pharmacological interventions, dietary suggestions and several behavioural strategies, such as nutritional counselling and cognitive behaviourally-oriented programmes [5-7].

The assessment of resting energy expenditure (REE) can play an important role in the management of these patients, consenting the quantification of the energy necessary to reduce excessive weight gain and obesity.

REE is usually calculated in the general population with predictive formulae (i.e., Harris-Benedict, Mifflin-St. Jeor, or LARN equations) based on age, stature, body weight and gender. The reliability of such predictive formulae for patients with psychiatric disorders has been recently disputed, especially for patients with eating disorders [8]. To our knowledge, very few studies have systematically investigated the reliability of these formulae to calculate REE in patients who are taking psychotropic medications [9 10].

Indirect calorimetry (IC) has been proposed to overcome the potential limits of predictive formulae when they are applied to special populations of patients, which measures oxygen consumption and production of carbon dioxide [11]. To our knowledge, few studies have measured REE with the IC devices on patients with bipolar disorder [12-14].

The aim of this study was to compare the REE obtained us-

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ing a portable metabolic IC device (VO2000) with those calculated by the Harris-Benedict, Mifflin-St. Jeor and LARN equations in a cohort of patients undergoing stable psychopharmacological treatment for at least 6 months, and who were already followed-up in a naturalistic setting dedicated only to females with bipolar I disorder. We were interested in determining whether IC and predictive formulae could be considered as alternative methods for assessing REE in a clinical sample different from the general population.

Subjects

Seventeen female subjects with bipolar I disorder consecutively admitted to the outpatient section of the Psychiatric Clinic of the University of Pisa, Italy, between July 2004 and June 2008, were enrolled. Diagnosis of Bipolar I disorder was made according to the DSM-IV criteria, as listed in the SCID-IV section dedicated to mood disorders. Patients with psychiatric comorbidity were included in the study. Only one patient met diagnostic criteria for a second psychiatric disorder, namely obsessive-compulsive disorder (OCD).

All participants were provided with a complete description of the study, and gave written informed consent for participation, in accordance with the institutional requirements of the Azienda Ospedaliero-Universitaria Pisana. Patients with medical diseases interfering with metabolism (i.e., hypo/hyper-thyroid's functioning, pituitary diseases, diabetes, adrenal gland diseases), acute inflammatory states (e.g. infections), or chronic autoimmune disease were not enrolled.

Measurements

Data collection included weight and height measurement and IC with the portable metabolic calorimeter VO2000. The predictive regression equations of Harris and Benedict (1919) for current body weight (CBW) [15], LARN (1987) [16] and Mifflin-St. Jeor (1990) [17] were used to calculate REE.

Body weight and height

A physician involved in the study measured body weight on a medical balance and height with a stadiometer. Patients were standing, with heels together, arms to the side, legs straight, shoulders relaxed and head on the horizontal plane (looking straight ahead). Patients were weighed standing in the middle of a monthly-calibrated digital scale, wearing only underwear and without shoes, before breakfast. BMI was determined according to the usual formula of body weight divided by the square of height in meters.

Indirect Calorimetry

IC was performed at room temperature in a single session before breakfast using the VO2000 a portable metabolic measuring system. For this study, patients were asked to abstain from smoking, eating and drinking caffeinated and alcoholic beverages for at least 12 hours before the session, and to not perform physical exertion before the test. Upon arrival in the test room, patients were placed in a comfortable position on a medical seat, while the instrument was prepared immediately before measurements. The VO2000 uses an auto-calibration mode that calibrates the analysers using room air and proprietary software. The VO2000 uses a three-point harness system or single belt configuration for data collection in a field setting. The O2 analyser is a galvanic fuel cell with an accuracy of ±0.1%, while the CO2 analyser is a NDIR analyser with an accuracy of ±0.2%. The preVent pneumotach measures ventilation from expiratory flow volumes. A neoprene facemask used during data collection has an aluminium nosepiece that is adjusted at the bridge of the nose, a silicone coupler in front of the mouth for attaching the pneumotach and two strips of neoprene with Velcro to secure the facemask to the crown and nape of the neck.

Statistical analysis

Data are presented as means and standard deviations (SDs) for continuous variables and percentages for discrete variables. The associations between BMI and the measured and predicted REEs were analysed using Spearman correlation coefficients to take into account the skewed distribution of some variables. The Bland-Altman method [18] was used to study concordance between the VO2000 method with the Harris-Benedict, Mifflin-St. Jeor and LARN equations. The z-test was used to evaluate whether the mean of the differences between the values obtained by the three methods, with respect to VO2000, was or was not significantly different from zero. Furthermore, the Wilcoxon Signed-Ranks Test was performed to compare the mean REE values of the VO2000 method with those of the Harris-Benedict, Mifflin-St. Jeor and LARN equations. Statistical analyses were performed with SPSS 15 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Table I shows the demographic and clinical characteristics of the study sample. The mean age was 37 years and mean BMI was 28.8, ranging from 21.4 to 41.5, with 64.7% of the patients having a BMI ≥ 25, and 29.4% having a BMI ≥ 30.

TABLE I.
Anthropometric and clinical characteristics of the sample (n = 17). *Caratteristiche antropometriche e cliniche del campione (n = 17).*

Anthropometrics	Mean (SD)	Range
Height (cm)	166.1 (7.5)	155.0-184.0
Weight (kg)	79.5 (15.2)	57.0-105.5
Body Mass Index (kg/m^2)	28.9 (5.7)	21.4-41.5
Age (yr)	37.3 (11.4)	21.0-57.0
Resting Energy Expenditure		
VO2000 (kcal/day)	1122.1 (228.6)	790.0-1500.0
Harris-Benedict equation (kcal/day)	1547.8 (156.7)	1356.9-1809.4
Mifflin-St. Jeor equation (kcal/day)	1485.3 (177.9)	1295.0-1788.0
LARN et al. equation (kcal/day)	1559.3 (168.7)	1333.9-1863.1

TABLE II.
Atypical antipsychotics and mood stabilisers administered. *Antipsicotici atipici e stabilizzatori dell'umore somministrati ai pazienti.*

Patient #	Atypical Antipsychotic	Dosage (mg/day)	First Mood Stabilizer	Dosage (mg/day)	Second Mood Stabilizer	Dosage (mg/day)
1	Olanzapine	5	Oxcarbazepine	300	-	-
2	Olanzapine	3.75	Lithium	900	-	-
3	Olanzapine	7.5	Lithium	750	-	-
4	Olanzapine	10	Valproate	1200	-	-
5	Olanzapine	5	Carbamazepine	300	-	-
6	Olanzapine	15	-	-	-	-
7	Olanzapine	2.5	Lithium	600	-	-
8	Olanzapine	5	Valproate	500	-	-
9	Olanzapine	5	Valproate	1000	-	-
10	Olanzapine	2.5	Lithium	600	-	-
11	Olanzapine	5	-		-	-
12	Quetiapine	25	Lithium	750	Valproate	600
13	Aripiprazole	15	Pregabalin	225	-	-
14	Aripiprazole	2.5	-	-	-	-
15	Quetiapine	100	-	-	-	-
16	Quetiapine	100	Lithium	300	-	-
17	Aripiprazole	10	Lithium	600	Valproate	750

Table II summarizes treatments with atypical neuroleptics and mood stabilisers at the time of measurements. Figure 1 shows the Bland-Altman plots reporting the differences between REE values measured with VO2000 and those obtained using the other methods (Harris-Benedict, Mifflin-St. Jeor and LARN equations).
The mean of the differences between the REE values estimated with the Harris-Benedict equation and those measured with VO2000 (bias = 425.6 kcal/day) was significantly different from zero ($t = 8.48$; $p < 0.001$). Moreover, for the other two comparisons, the means of differences between Mifflin-St. Jeor method and VO2000 method was significantly different from zero (bias = 363.2 kcal/day; $t = 6.29$, $p < 0.001$) and also between LARN equation and VO2000 method (bias = 437.2 kcal/day, $t = 7.34$, $p < 0.001$).

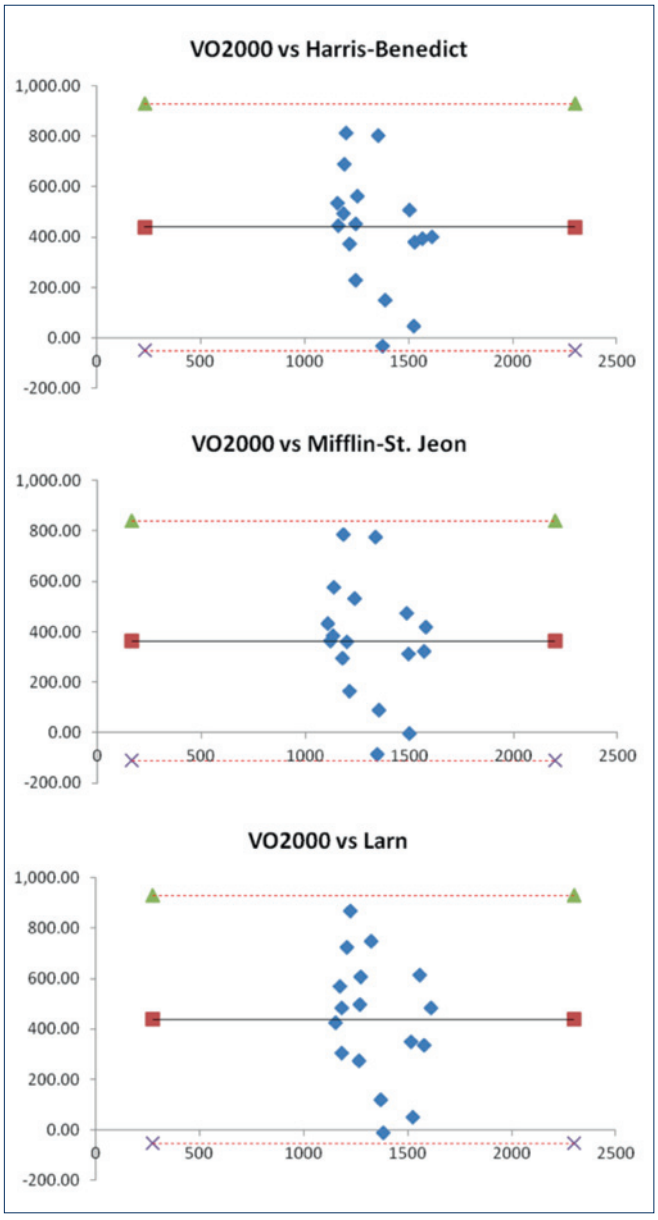

FIGURE 1.
Bland-Altman plots comparing the three methods of measuring REE considered together with IC. *Bland-Altman Plots che comparano i 3 metodi di misurazione del REE con la calorimetria indiretta.*

BMI was significantly correlated to REE measured using Harris-Benedict (rho = 0.77, p < 0.001), Mifflin-St. Jeor (rho = 0.69, p = 0.002) and LARN (rho = 0.78, p < 0.001) equations, but was not correlated to REE measured using the VO2000 method (rho = 0.08, p = 0.747).
The measured REE was not significantly correlated with the three methods (Harris-Benedict rho = 0.23, p = 0.376; Mifflin-St. Jeor rho = 0.24, p = 0.360; LARN rho = 0.17, p = 0.501).

The Wilcoxon Signed-Ranks Test showed significant differences between the mean REE values estimated with the VO2000 method and the mean values estimated with Harris-Benedict equation (Z = -4.23, p < 0.001), Mifflin-St. Jeor equation (Z = -4.06, p < 0.001) and LARN equation (Z = -4.17, p < 0.001).

Discussion

Our data indicate that the Harris-Benedict, Mifflin-St. Jeor and LARN equations overestimated REE in female patients with bipolar I disorder. The overestimation of REE using the above-mentioned equations in our sample was relatively consistent, and close to 400 kcal/day from the predicted REE value. A possible reason for the high overestimation error in the prediction of REE with the Harris-Benedict, Mifflin-St. Jeor and LARN equations is that they are tested in the nutrition field on the general population. Conversely, patients with bipolar I disorder are chronically in a significantly different condition compared to the general population. Bipolar disorder is characterised by extreme variations in mood, energy and in psychomotor activation *versus* retardation when bipolar patients shift from manic/mixed to depressive episodes. For example, abundant resources of energy characterise manic episodes; the increased physical activity has a significant impact on energy expenditure, accounting for 20–30% of the body's energy output [19]. A recent study suggested REE as a possible biological marker in the manic episodes of bipolar I disorder, considering the relevance of its variations when a manic/mixed episode occurs [14]. Given that, we evaluated only patients stabilised on medications for at least six months to avoid acute episodes that may have affected their energy expenditure. However, a stable condition requires long-term treatment with several psychotropic medications that have a profound impact both on metabolism and eating habits, as already noted by Skouroliakou and colleagues (2009) [10]. Our finding is concordant with that of Sharpe and colleagues (2005) [9] who reported that the Harris-Benedict equation overestimated the REE in a group of male patients taking clozapine. Nonetheless, there are several differences between the two studies, considering Sharpe's sample selection (only male patients) and the choice of enrolling patients who were taking clozapine. Thus, even if olanzapine and clozapine are both included in the same class of drugs, they have different receptor affinity profiles, and clozapine is considered as second-line treatment, when other antipsychotics (such as olanzapine) have already failed [20]. None of our female patients was taking clozapine. Our data are partially in line with Skouroliakou and Colleagues [10] who found that the Mifflin-St. Jeor and Harris-Benedict equations for adjusted body weight were accurate in estimating the energy needs of a sample of patients treated only

with olanzapine. However, the Harris-Benedict current body weight and Schofield equations showed significant overestimation error in the REE prediction ($p < 0.001$). Skouroliakou and Colleagues [10] concluded that the possible reasons for the high overestimation error in the prediction of REE with equations such as the Harris-Benedict and Schofield were the specific characteristics of this population, namely the effects of mental disease, antipsychotic medication use, mood changes and alterations in psychosocial rhythm. Nonetheless, they did make a narrow selection of patients, enrolling only those who were obese (body mass index > 30 kg/m^2) and treated with olanzapine. Patients in our sample were treated with olanzapine, quetiapine, aripiprazole and no selection was made on BMI. In general, there is a strong correlation between BMI and percentage of body fat. The positive relationship between energy expenditure and BMI has been previously reported [21]. In our study, we found a significant correlation between BMI and measured REE, but not between BMI and predicted REE, confirming the weakness of the predictive formulae in measuring REE in female patients with bipolar I disorder.

The main limitations of this study are the small sample size and the absence of a control group. Moreover, we are aware that a more refined measurement of metabolism should take into account several additional parameters, including urinary ammonia nitrogen, total nitrogen levels and body composition. However, these parameters were not included, considering the naturalistic setting of this preliminary study.

Conclusions

Our findings suggest that commonly-used formulas may not be considered as an alternative to the VO2000 method for assessment of REE in patients with bipolar I disorder. Clinicians are well aware that patients with a Bipolar Disorder are at higher risk than the general population for obesity and metabolic syndrome. Nonetheless, a resting energy expenditure assessment that includes IC is still lacking in the routine outpatient setting. We propose that IC become part of routine clinical evaluation when patients with bipolar disorder are followed-up, considering that formulae are not specific for this special population. Despite the limitations mentioned, our results are of interest because they demonstrate the feasibility and acceptability of a simple intervention in patients receiving psychotropic medications, who are usually concerned about the metabolic consequences of long-term treatment. Moreover, we agree with previous observations on the importance that REE studies in bipolar patients have for clinicians. For example, as suggested by Caliyurt and Altiay (2009) [14] the REE measurements might help psychiatrists to monitor bipolar patients in remission and to detect the development of manic episodes as they are characterised by increased energy levels that could be identified earlier if repeated REE measurements are performed.

Finally, we believe that future studies using gold-standard methods to assess REE in samples of patients with Bipolar disorder should take into account the different forms of Bipolar Disorders, including bipolar II Disorder, cyclothymic disorder and sub-threshold syndromes belonging to the overall spectrum of mood disorders [22].

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None.

Conflict of interests
None.

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Testing three theories of cognitive dysfunction in alcohol abuse

Analisi dei deficit neuropsicologici alcol-correlati alla luce di tre differenti ipotesi teoriche

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Summary

Objectives

Many hypotheses concerning the cognitive functions affected by chronic alcoholism have been advanced. The aim of this study was to test cognitive performance in a sample of alcoholics and to examine results comparing three different models: the frontal lobe hypothesis, the lateralisation hypothesis and the diffuse brain hypothesis.

Methods

Fifty-one patients who referred to an alcoholism service were included in this study. Cognitive functions were assessed by a trained psychologist using a specific neuropsychological battery.

Results

Our results show a ranking of degrees of impairment in different cognitive functions with dissimilar influence on clinical features. In our sample, the frontal lobe hypothesis was disconfirmed. The results on right hemisphere seem to require more investigation and the generalized deficit hypothesis was not confirmed.

Conclusion

Cognitive deficits may compromise patients' utilisation of rehabilitative information. Increasing attention is being given to the opportunity to integrate specific support for cognitive functions in alcohol detox programmes. The first step in programming clinical intervention is to have a complete overview of the cognitive deficits in alcoholics.

Key words

Alcoholism • Cognition • Impairment • Theories • Cerebral lobes • Clinical features

Introduction

Alcohol abuse is a maladaptive pattern of drinking, leading to clinically-significant impairment or distress, as manifested by at least one of the following occurring within a 12-month period:

- recurrent use of alcohol resulting in a failure to fulfil major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to alcohol use; alcohol-related absences, suspensions, or expulsions from school; neglect of children or household);
- recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by alcohol use);
- recurrent alcohol-related legal problems (e.g., arrests for alcohol-related disorderly conduct);
- continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol (e.g., arguments with spouse about consequences of intoxication) [1].

Research on alcoholism has two important aims: to evaluate existing therapies and to increase knowledge about the biology of alcoholism. Heavy alcohol intake is associated with both structural and functional changes in the central nervous system, with long-term neuronal adaptive changes contributing to the phenomena of tolerance and withdrawal symptoms [2]. Considerable progresses has been made in the last 20 years regarding the physical mechanisms of addiction, theories of alcohol action in the human body and psychosocial effects of alcohol abuse [3]. Despite these facts, it is still difficult to have a general view of the above knowledge since alcohol dependence is a heterogeneous disorder with many contributing factors that vary from person to person [4]. Several studies have shown important variations in the presence and severity of different cognitive deficits. In fact, there is a gap between patients who do not present any kind of disorder and those who develop dementia [5].

The exact nature of the neuropsychological disorders related to alcoholism is still under discussion. New neuro-

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science techniques have led to an increased understanding of alcohol addiction and have permitted studies of the effects of alcohol on the brain. Both animal and human genetics studies are increasingly enabling the identification of genes that confer vulnerability to alcoholism. Issues requiring a great deal of further study include individual drinking patterns, the role of cognition in alcohol-seeking behaviour and the subjective effects of drinking [6].
The causes of cognitive impairment found in alcoholics include direct effects of alcohol toxicity, pre-existing cognitive deficits that predispose towards substance abuse, comorbid psychiatric disorders and abuse of substances other than alcohol [7].
Studies on neuropsychological functions in alcoholism have reported different deficits including visual-spatial abilities, attention, memory, executive function and social cognition [8]. In particular, visual-spatial and explicit memory for visual-spatial stimuli deficits has been observed [9].
Greater deficits in executive functions compared with other cognitive functions have been reported, especially in problem solving, abstraction, planning, organising and working memory [10]. Working memory has been investigated in several studies and impairments have been often found [11]. For Hildebrandt, the neurotoxic side effects of alcohol therefore lead to a specific deficit in alternating between response rules but not in working memory, independently of whether the working memory task involves interferences resolution or not [12]. A study conducted in a Spanish sample showed poorer performance in tests related to attention control, performance speed, automatic response inhibition, visual-spatial function and visual memory [13]. A representative sample of alcoholics showed specific attention deficits as opposed to a general decline of attention at treatment intake. Thus, sober alcoholics appear to be as efficient as controls at selecting on the basis of location. Nonetheless, when they are required to respond to two independent sources of information, such as the divided attention task, they show impaired performance [14]. Previous studies are discordant on cognitive impairment in alcoholism: for example, in younger samples, cognitive impairment is more infrequent [15]. One of the most important goals of the evaluation is the recovery of cognitive deficits related to alcohol abuse; several cognitive deficits (perceptual motor speed, verbal short-term memory, verbal knowledge, non-verbal reasoning and spatial imagination) show significant improvement after 5 weeks of treatment [16]. Similar results have been found in an Australian sample: at baseline, chronic and episodic alcohol users showed impaired visual motor, learning, memory and executive function. Visual motor deficits had normalised within 11 months and other deficits had improved to normal levels within 4 weeks [17]Throughout many studies educational attainment is only sometimes controlled, and is thus problematic. Krahn hypothesised that the observed relationship between alcohol intake and cognition may change when this variable is controlled [18]. Moreover, alcoholics achieve significantly lower scores that controls on summery indices of the Wechsler Memory and Adult Intelligence Scales and showed greater decline from estimated premorbid intelligence levels than controls [19]. High level cognitive processes are also an important field of research. Some theories of mind and deficit in executive functions have been found and could be of relevance in investigating their impact on rehabilitation programmes [20].
The exact nature of the neuropsychological disorders related to alcoholism is still under discussion and the most recent investigations have proposed different hypotheses. The first hypothesis is known as "frontal lobe" hypothesis and states that the frontal lobes are most vulnerable to the effects of alcohol. There is agreement upon the specificity of cognitive functions related to the frontal lobe, called "executive functions" [21]. More precisely, these functions include: cognitive flexibility, speed in allocation of attentional resources, shifting ability, speed in information processing, inhibition of perseverative errors, perceptual motor speed, abstractive and planning abilities and suppression of irrelevant information. Findings in alcoholicssuggesting deficits on abstracting and problem solving tests, support this hypothesis. Difficulties in categorising and inflexibility of thinking, as measured by different instruments, could be related to selective frontal lobe dysfunction, even in the absence of severe global impairment [22-23].
In support of the frontal lobe hypothesis, findings from multiple neuropsychological studies have revealed diminished functioning in problem solving, abstraction, working memory, attention and response inhibition/impulsivity [24-29]. Different studies have demonstrated a loss of neurons, primarily from the frontal cortex [30-34]. These studies suggest that the frontal lobes are more susceptible to ethanol damage than other brain regions. However, other studies have either found a lack of dysfunction in the frontal lobes or have revealed deficits in other regions, negating the hypothesis of frontal lobe exclusivity [35-37]. These contrasting findings require further investigation.
The second hypothesis is the "lateralisation hypothesis", which states that right hemisphere functions are more susceptible to the neurotoxic effects of alcoholism [38]. The right hemisphere has a role in selective attentional processing and has the ability to attend to the spatial array. The pattern of results in alcoholics is consistent with the right hemisphere model of alcoholism-related cognitive decline [39].
Comparison between verbal and non-verbal tasks has shown that impairment of visual learning, visual memory and visuospatial abilities are often be found and seem to be more resistant to recovery [40-42].

The "diffuse brain dysfunction" hypothesis considers that alcohol affects all areas of the brain. A review by Parsons [43] described findings from cross-sectional and longitudinal studies; these results revealed verbal, visuospatial and abstracting deficits that support the diffuse brain hypothesis. The cognitive deficits showed by sober alcoholics include impairment in different functions, such as verbal and non-verbal thinking, verbal and non-verbal learning, memory, visuospatial perception and perceptual motor skills [44 45]. This pattern of deficits is consistent with the hypothesis that chronic alcoholism produces mild generalised brain dysfunction.

While studies frequently make allusion to each of these three hypotheses, inconsistent findings have been reported that do not always support the assumptions of one specific theory. The aim of this study was to test cognitive performance in a sample of alcoholics and to examine the results to compare these different models.

Methods

Participants

A total of 110 alcohol-dependent individuals were consecutively recruited from the alcohol-dependence service of San Raffaele Hospital in Milan, Italy at admission.

All subjects were given an assessment, which took approximately three hours and included an anamnestic interview and a neuropsychological battery that was administrated by trained technicians of the psychological service within the first week after admission, or as soon as the patient was clinically stable enough to undergo testing.

Patients who had previously been diagnosed with any disorder from DSM-IV TR Axis 1 (other than substance dependence) were not included. Moreover, patients with concurrent neurological diseases and traumatic brain injury were excluded as were those with a MODA score < 89 (30 patients were classified as insufficient).

The final sample included 51 subjects (33 men; 18 women), aged between 27 and 69 years old (47.00 ± 9.88) with school attendance that ranged from 6 to 18 years (12.67 ± 3.18). The concurrent use of substances other than alcohol was also evaluated: 37.2% of patients (n = 19) have reported no substance use, 54.9% of the sample (n = 28) referred substance use in the past and 7.9% (n = 4) were using substances at admission.

All participants were native Italian speakers and accepted the informed consent. No remuneration was given. The study protocol was approved by the hospital's ethics committee.

Procedures

Measures

The neuropsychological battery included Brief Assessment of Cognition in Schizophrenia (BACS) and Milan Overall Dementia Assessment (MODA). BACS includes the following subtests: verbal memory (word recall); working memory (digit sequencing); token motor task (psychomotor speed and coordination); selective attention (symbol coding); semantic fluency; letter fluency; Tower of London. Verbal memory tasks were adapted to Italian by substituting English words with Italian words that were matched for frequency and phonemic characteristics. The letter fluency tasks were adapted using letters that were already used in common Italian clinical tests for letter fluency. Verbal memory and Tower of London tasks consist of two alternative forms for repeated measures assessment [46]. The BACS scores were analysed by simultaneous multiple regression to assess the influence of age, education and gender. For each score, a linear regression model was applied to adjust original score for age, education and gender. The cut-off score indicates the score below which the probability than an individual belongs to the normal population is less than 0.05, with a confidence level of 0.95. Norms were computed with the equivalent scores method [47] to enable comparison with other neuropsychological tasks commonly used in Italy [48-50], such as Wisconsin card sorting test, Stroop colour-word tests and Raven's progressive matrices. Adjust scores were fitted into a 5-point interval scale to obtain equivalent score, that was classified as follows: limit for pathological performance = 0; borderline value = 1; intermediate value = 2 or 3; equal or better than median value = 4 [51].

MODA is a short, neuropsychological oriented test used for assessment of dementia. MODA is a paper and pencil test composed of three sections: a behavioural scale and two testing sections. The three sections are given in the same testing session in the same sequence. The behavioural component (autonomy scale) accounts for 15% of the score and comprises a set of items that assess everyday coping skills. Information is provided by a relative and can therefore be collected even in cases of severe deterioration. The cognitive contribution represents 85% of the total score (orientation enquiry and neuropsychological testing yield, respectively, 35% and 50% of the overall score). The MODA total score ranges from the worst of 0 to the best of 100. In all items, a score of zero is given if the patient fails to provide an answer or responds inappropriately. Instructions may be repeated for each item, so as to elicit the patient's best possible performance [52].

Results

Descriptive statistics

Table I shows the descriptive statistics of the subtest score considering the different grade of impairment in cognitive functions. Equivalent scores allow considering scores 0 and 1 as "deficient". These results demonstrate the dissimilar grades of impairment between the different cognitive functions.

In each BACS subtest, correction grids were used to adjust the performance of each subject in term of education, age and sex. Single subtest scores are shown in Table I.

Considering equivalent score it is possible to state that, in our sample, the lowest-scoring functions are attention and speed of information processing, which had mean of 1.47 ± 1.50. Motor speed and coordination had mean of 1.90 ± 1.50; these results appear to confirm the relationship between alcohol abuse and low functioning of the motor system. Verbal fluency showed a mean of 2.12 ± 1.27.

Verbal memory and working memory had higher results than other functions with means of 2.74 ± 1.41 and 2.47 ± 1.28, respectively. The Tower of London task showed the highest results and the lowest dispersion with mean of 3.33 ± 1.11.

Table II shows that age had a significant relationship with

TABLE I.
Descriptive statistics. *Statistiche descrittive.*

	Min.	Max.	Mean	S.D.	Median	Interquartile range	Percentages of deficient participants (e.s.0 + e.s.1)
Verbal Memory Correct Score	27.75	67.75	47.40	10.39	48.75	18.00	-
Verbal Memory E.S.	0.00	4.00	2.74	1.41	3.00	3.00	27.5%
Working Memory Correct Score	12.50	31.25	20.63	4.38	20.25	6.25	-
Working Memory E.S.	0.00	4.00	2.47	1.29	3.00	3.00	27.5%
Motor Speed Correct Score	44.00	100.00	76.94	14.83	77.75	22.00	-
Motor Speed E.S.	0.00	4.00	1.90	1.50	2.00	2.00	45.1%
Verbal Fluency Correct Score	26.25	68.50	44.47	9.72	45.25	14.75	-
Verbal Fluency E.S.	0.00	4.00	2.12	1.27	2.00	2.00	33.3%
Attention and speed of processing Correct Score	27.00	77.50	45.75	11.72	43.75	15.75	-
Attention and speed of processing E.S.	0.00	4.00	1.47	1.50	1.00	3.00	58.8%
Tower of London Correct Score	10.00	22.50	18.60	3.15	19.00	4.00	-
Tower of London E.S.	0.00	4.00	3.33	1.11	4.00	1.00	11.1%

Min.: minimum score; Max.: maximum score; S.D.: standard deviation; E.S.: equivalent score.

TABLE II.
Impact of clinical features. *Impatto delle caratteristiche cliniche.*

Function	Age	Education	Other substances abuse	Sex
Verbal Memory ES	n.s.	n.s.	n.s.	n.s.
Working Memory ES	n.s.	n.s.	n.s.	n.s.
Motor Speed ES	-0.366 ($p < 0.01$)	n.s	n.s.	n.s.
Verbal Fluency ES	n.s.	n.s.	n.s.	n.s.
Attention and speed of information processing ES	n.s	0.343 ($p < 0.05$)	n.s.	n.s.
Tower of London ES	n.s.	n.s.	n.s.	n.s.

E.S.: equivalent score; n.s.: non significant.

motor speed and coordination. Education had a direct relationship on attention and speed of information processing. Polyabuse condition did not show any impact on cognitive performance in comparison with only alcohol abuse alone. the was no association of gender with cognitive performance.
Correlations were used to assess the effect of age and education because it was not possible to assume population discontinuity in specific classes. Age had a significant relationship with motor speed and coordination, and the worst performances were found in older patients (correlation: -0.37). Education had a direct relationship on attention and speed of information processing (correlation: 0.34).
The Mann-Whitney non-parametric test allows us explore the impact of dicotomic variables as polyabuse and sex on cognitive performance. As there were no significant differences, this suggests that polyabusers do not have worse cognitive performance in comparison with alcoholics alone. Gender had no relationship with cognitive functions.

Comparison of different cognitive functions

To evaluate the differences within the different cognitive function, in order to determine which hypothesis is the most reliable, we applied Friedman's ANOVA on the equivalent score totalised in the assessment session using the BACS battery. To evaluate the post-hoc test, we utilised the Wilcoxon test, adjusting the confident interval by Bonferonni's methodology ($\alpha = 0.05/5 = .01$).
Frontal Lobe Hypothesis: we have compared the Tower of London equivalent score with other cognitive performances to determine if the frontal functions were the most deteriorated, according to the hypothesis mentioned earlier. The Tower of London showed an equivalent score that was significantly higher than all other cognitive functions (Tab. III). Therefore, is possible to conclude that frontal functions are less impaired in alcohol dependent patients, refuting the frontal lobe hypothesis.

TABLE III.
Frontal lobe hypothesis. *Ipotesi dei lobi frontali.*

Tower of London E.S. *vs.*	Z	p
Verbal Memory E.S.	-3.12	$p < 0.01$
Working Memory E.S.	-3.87	$p < 0.001$
Motor Speed E.S.	-4.92	$p < 0.001$
Verbal Fluency E.S.	-4.34	$p < 0.001$
Attention and speed of information proc. E.S. sing. E.S.	-5.56	$p < 0.001$

E.S.: equivalent score. A negative Z score indicates that it is higher than the score with which it has compared.

TABLE IV.
Lateralisation hypothesis. *Ipotesi della lateralizzazione.*

	Z	p
Verbal Memory E.S. *vs* Verbal Fluency E.S.	-2.11	$p > 0.01$ (n.s.)
Verbal Memory E.S. *vs* Motor Speed E.S.	-2.98	$p < 0.01$
Verbal Memory E.S. *vs* Symbol Coding E.S.	-4.95	$p < 0.001$
Verbal Fluency E.S. *vs* Verbal Memory	-2.11	$p > 0.01$ (n.s.)
Verbal Fluency E.S. *vs* Motor Speed E.S.	-0.88	$p > 0.05$ (n.s)
Verbal Fluency E.S. *vs* Symbol Coding E.S.	-2.82	$p < 0.01$

E.S.: equivalent score; n.s.: non significant. A negative Z score indicates that it is higher than the score with which it has compared.

Table III shows the that the Tower of London equivalent score was significantly higher than all the other cognitive functions Therefore, is possible to conclude that the frontal functions are less impaired in alcohol dependent patients, negating the frontal lobe hypothesis.
For the lateralisation hypothesis we compared the results of verbal and non-verbal tasks. Verbal tasks were measured by the subtests of Verbal Memory and Verbal Fluency, while the non-verbal tasks were represented by the Motor Speed and Symbol Coding subtests. The results only partially confirm the lateralisation hypothesis. Verbal memory showed significantly higher results than non-verbal tasks. Verbal fluency had no significant association with motor speed (Tab. IV).
Table IV shows that verbal memory had significantly higher results than non-verbal tasks. Verbal fluency had no significant differences with motor speed.
For the diffuse brain dysfunction hypothesis we have compared the results of all tasks in order to determine if all cognitive functions had the same level of impairment according to the above-described hypothesis (Tab. V). While it was possible to rank degree of impairment in different cognitive functions, the results are in contrast with the diffuse brain dysfunction hypothesis.
Table V shows that different cognitive functions are affected to various degrees by alcohol intake. It is not possible to confirm the diffuse brain dysfunction hypothesis.

Discussion

Cognitive impairment is a core feature of chronic alcoholism. Between 50% and 80% of individuals with alcohol use disorders experience mild to severe neu-

TABLE V.
Diffuse brain dysfunction hypothesis. *Ipotesi di deficit diffuso.*

	Z	p
Working Memory *vs* Verbal Memory ES	-1.31	n.s.
Working Memory *vs* Motor Speed ES	-2.69	p < 0.01
Working Memory *vs* Verbal Fluency ES	-1.92	n.s.
Working Memory *vs* Symbol Coding ES	-4.15	p < 0.001
Motor Speed ES *vs* Symbol Coding ES	-1.93	n.s.

E.S.: equivalent score; n.s.: non significant. A negative Z score indicates that it is higher than the score with which it has compared.

rocognitive impairment. Current treatments for alcohol abuse disorders focus on changing behaviour and developing skills to prevent relapse and promote psychosocial adaptation, activities that clearly require cognitive processing [53-56]. The relationship between cognitive impairment and alcoholism treatment is still under discussion. Clinical experience suggests that alcohol-related neuropsychological impairment affects treatment outcome, but research on addiction have provided few indications in this direction. Bates, Bowden and Barry have explored this aspect by testing five different models of the relationship between neuropsychological impairment and addiction treatment outcome [57]. Their finding do not support a direct influence of cognitive impairment on outcome, but suggest that it could be a moderator variable which impacts the action and strength of risk factors.

The principal aim of this study was to investigate the theoretical framework explaining cognitive impairment related to alcohol abuse by testing different hypotheses in a clinical sample.

The descriptive analysis allowed us to compare single subtest scores and to use them to investigate different hypotheses. It was possible to conclude that the scores in executive functions task (Tower of London task) are significantly higher than the one in other functions; Verbal Memory is the second less impaired function, with significant differences in motor speed, attention and speed of information processing. The third most preserved function is Working Memory. In contrast, the most impaired functions include Attention and Speed of information processing, and show significantly lower scores than Tower of London, Verbal Memory and Working Memory tasks. Motor speed showed a significantly lower level than London Tower and Verbal Memory task, and Verbal Fluency had lower significantly scores only compared to Tower of London, which showed significantly higher scores than other functions.

This result underlines that frontal functions are the most resilient to alcohol damage and do not confirm the frontal lobe hypothesis. These results thus require a further investigation.

In order to test the lateralisation hypothesis, we compared verbal and visual-spatial functions. Verbal memory showed a higher score than both psychomotor speed and symbol coding tasks. These results would seem to confirm the lateralisation hypothesis, although verbal fluency had no significant differences with visual-spatial functions. Therefore, the lateralisation hypothesis cannot be completely confirmed.

Our results show significant differences between the BACS subtests. It is possible to rank different degrees of impairment in different cognitive functions, and the results are in contrast with the diffuse brain dysfunction hypothesis, which considers the same level of impairment between different functions. Speed of processing, verbal fluency, psychomotor speed and coordination seem to be most impaired functions; these abilities presume the presence of preserved executive speed. These results appear to be in agreement with the hypothesis that alcohol significantly slows total information processing.

The results of the present study must be considered in light of several limitations. The small size of our sample could influence the possibility of generalising our conclusions. The absence of a control group is due to the aim of this study: in fact, our principal purpose was to compare different hypotheses about the exact nature of neuropsychological disorders related to alcoholism. The small size of our sample makes it difficult to attribute the results to alcohol consumption; otherwise, the equivalent score method assumes that the corrections based on normative sample are applicable to small samples and, in addition the influence of principal clinical features (i.e. age, sex, scholarship and polyabuse) on cognitive performance must be taken into consideration.

The relationship between cerebral lobes and neuropsychological measures shows complex patterns; cerebral lobes are multifunctional structures and a single neuropsychological measure could seem inadequate to test their functioning. Nevertheless, our results are supported by findings in the literature. The Tower of London task is thought to depend on planning ability, a capacity requiring intact frontal-lobe functioning.

Comparing Korsakoff and non-Korsakoff alcoholics, Joyce and Robbins have demonstrated that only Korsakoff patients show impairment in this task. Moreover, the deficit in Korsakoff patients in this task is not due to impairment in visuospatial skills or memory, but to impairment in planning ability [58]. Smith and Jonides, using a threshold-independent measure of hemispheric lateralisation, demonstrated that brain activity during verbal working memory showed a more left-hemisphere lateralised pattern of BOLD response, par-

ticularly in the frontal and parietal lobes, while spatial working memory invoked a pattern of more right-hemisphere lateralised activity, observed in both frontal and temporal lobe regions. This pattern is consistent with the literature in adults showing this hemispheric distinction [59].

Many authors have recently pointed out the necessity of considering intervenient phenomena during cognitive assessment. Cohen and Maunsell underline that it is impossible to control a subject's internal state completely, so that fluctuations in cognitive states, such as attention, must occur in all experiments [60]. The experimental evidence suggests that mind-wandering may be one of the most ubiquitous and pervasive of all cognitive phenomena. Taking into account multiple tasks, verbal reports have indicated that participants seem to spend 15-50% of the time mind-wandering. The possible relationship between mind-wandering and our results will be considered in a future study.

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Conflict of interests
There is no conflict of interest.

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The metacognitive functioning in schizophrenia: a proposal for assessment

Il funzionamento metacognitivo della schizofrenia: proposta di valutazione

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Summary

Several studies have highlighted many metacognitive deficits in patients with schizophrenia.

The concept of metacognition refers to all those abilities that are needed to understand one's own or someone else's thoughts and affections, and refers also to the process of reflection on mental states that allows to use such information to solve psychological or interpersonal conflicts. Thus, metacognition includes a series of semi-independent abilities that could be damaged separately or in combination. Due to the multi-dimensional nature of the construct, in this survey we suggest a battery of tests, each test analyses different metacognitive functions. Furthermore, we propose an implementation of such battery through the presentation of results of two groups of patients with schizophrenia (characterized by different levels of inveteracy), and the comparison with a control group composed of healthy subjects. The implementation of this battery has highlighted the presence of metacognitive impairments from the early onset of the disease, while the comparison between chronic patients and patients at the early onset of the disease shows a gradual impairment of such abilities.

Key words

Schizophrenia • Assessment • Hinting Test • Brüne Picture Sequencing Task • Reading the Mind in the Eyes test • Irony Task • Beck Cognitive Insight Scale

Metacognition in schizophrenia

During the last decades several studies have highlighted the presence of an impairment about specific abilities defined "metacognitive" [1-5]. In literature, the term "metacognition" coincides with other terms such as Theory of Mind (ToM) [6-10], social cognition [11], emotional awareness deficit or alexithymia [12-15], mentalization [16 17] and affective awareness [18]. The "metacognition" concept refers to the general ability of each individual to infer one's own and others' thoughts and affections and to the process of reflection on mental states that allows to use such representation in order to solve psychological and interpersonal conflicts [19-21]. Thus, metacognition includes a series of semi-independent abilities that could be damaged separately or in combination; for example, we can infer others' emotions through their facial expressions, but we have less sensitivity towards our own emotions. These metacognitive skills, not only can be activated separately but they also interact among them functioning like a system able to allow social adaptation and problem solving.

Patients with schizophrenia have strong metacognitive impairments: they have difficulty in distinguishing the origin of their inner experience; in perceiving themselves as able to actively affect what is happening around them; when they are involved in relationships they cannot understand others' implied intentions and emotions through visual and verbal signals, they are not able to build elaborate descriptions of themselves and others, as well as understanding their irony; and normally their speeches are characterized by poverty of contents and confusion [1 4 5 22-26]. Metacognitive impairments are a constitutive part of the disease [1] and they play a fundamental role for the onset and the maintenance of the disease [27 28]; they have a direct effect on social functioning, because they affect the abilities to engage in relationships and in social skills, in taking care of oneself and in keeping a working activity [29-34]; in general they agree to undertake the treatment [35].

These impairments seem to be a distinguishing feature of the disease, that is quite stable over the time [36] and they can be sharpened by the early onset of dysfunctional emotions and beliefs [37 38]. Due to the main role played by the metacognitive functioning within the schizophrenic disease, in this survey we are going to provide a battery of tests selected to assess such functioning; we did believe that a metacognition assessment must be considered for the definition of complex projects such as in the case of the so called difficult patients [39].

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Assessment of the metacognitive functioning

Despite the growing interest in the metacognition role during the last years, there is no agreement so far about which test can be considered the most suitable to evaluate such abilities. In schizophrenia metacognition is mainly studied in terms of ToM, showing a relevant correlation between ToM impairments and specific symptoms, for example the persecutory delusion [2 40-44].

Due to the multi-dimensional nature of metacognition, during its assessment it is better to include multiple tasks or tests to analyse the different functions. Some of these tests require that the subject makes some reasoning about others' mental states. Such tests are called "social-cognitive" and require the assimilation of contextual aspects about individuals (for example what some specific characters know and what they did, in order to infer their mental state) and they interact with other complex cognitive functions, like the language.

Some of these tasks assess the comprehension of others' mental states using vignettes or pictures sequencing [45 46]. These tests assess the subject's ability to infer the false beliefs of one of the characters of the story, or the false beliefs that a character of the story has about another character's mental state. In order to succeed in such tasks it is necessary for the subject to distinguish mental states and mental representations from the real world. Other similar tools demand the subject to complete stories where he has to infer the characters' intentions (AIT) [47]. Among the social-cognition tools, there are those that assess the subject's ability to understand the pragmatic language, in other words the ability to infer the meaning of others' speeches (for example tests that assess irony or the ability to understand metaphors). A good pragmatic skill implies the ability of going beyond the literal meaning of words to infer and evaluate the speaker's beliefs and intentions. Schizophrenic patients have problems in understanding both irony and metaphor use.

A second category of ToM tasks is the *social-perception* one; these tests investigate the patient's ability to infer mental states through implicit signals (for example by facial expressions or by the observation of bodily movements), and also using one's own automatic affective system. Probably the best know among these, is the Eyes Test [7 48] with which subjects are requested to choose which mental state best describes the photographs of the eye region they have been shown; schizophrenic subjects perform worse than healthy subjects [49].

Metacognition in schizophrenia has often been studied as a one-dimensional phenomenon, but the metacognitive acts have different sources and could involve skills that are conceptually separate [50]; as we have seen, the ability to understand one's own and others' mental state, among these there are the simplest skills, like the one that allows to understand the others' emotional expressions, or some others more elaborate, like the one that allows to keep a continuous representation of oneself in an integrated way. Therefore it is better to introduce multiple tasks to assess metacognitive abilities. Thus, during the assessment, it is necessary to use a series of tools that take into account the complexity of the metacognition construct.

Starting from these premises we have chosen some assessment tools, that were selected to answer to patient's needs as well as to the examiner's, within a clinic context like the schizophrenic one. Indeed, tests should not be onerous in terms of time and commitment, both for the patient (burdened by symptoms and by cognitive impairments during the performance) and for the examiner (normally a Services operator with heavy burden of work). We believe it is necessary to use a battery of tests and not only a single test, just because of the multi-dimensional nature of the metacognitive functioning; also to limit the methodological error due to the patients' heterogeneity of function: many of them shows different abilities in answering to verbal tests rather than iconic tests. Therefore, it is important to have the possibility to diversify the stimulus proposed with the test, in order to obtain a more complex evaluation, closer to that of the actual functioning. We suggest a battery of tests to assess the different metacognitive functions, that could be also easy to administrate, and that could be used with other tools, in order to observe how such functions interact with aspects that are closely correlated, like the social functioning, the subjectively perceived quality of life and the symptomatology aspects; so to have a "customized" definition of the complex treatment course of the schizophrenic patient.

The selected tests are the following. Two social-cognitive tasks have been selected to assess ToM abilities and the understanding of others' mental states, these tasks solicit such functions using different stimuli: *The Hinting Task* (pragmatic language comprehension) and the *Theory of Mind Picture Sequencing Task* (stories with picture sequencing). A social-perceptive task like the *Reading the Mind in the Eyes test* to assess the ability to understand others' emotions. We have also added a test like the *Irony Task*, to assess the abilities to infer others' intentions, and a self-report scale like the *Beck Cognitive Insight Scale*, to assess the self-reflection.

The tests

The *Hinting Task* [41] is a test that consists of 10 brief stories describing an interaction between two characters. Each story ends with one character giving a hint and the

participants have to infer the intention hidden behind the speeches; they are brief stories, in order to reduce the interference of memory or verbal comprehension problems. For example, story 10 is the following: Patricia is getting off the train with three heavy suitcases. John is standing behind her. Patricia says to John "Wow, these suitcases are a bother!". Each story is read aloud by the evaluator to the patient and they can be read as many times as needed to assure a correct understanding of them. At the end of each story the evaluator drops an easy and clear comment about the main character of the story. This is a useful hint for the subject who has to answer to the evaluator's question about the character's intentions. Regarding the story above for example, the evaluator will ask: "What does Patricia really want to say when she says this?". If the subject answers correctly 2 points are given, otherwise the evaluator makes a second comment to make the scenario clearer for the subject, and makes again the question; for example he could suggest "Patricia continues to say – I don't know if I can manage all 3 of them" and then he asks "What does Patricia want John to do?". If the subject answers correctly 1 point is given, if the answer is incorrect or he/she cannot answer, the score is 0. The task has a maximum score of 20 points and healthy adults normally reach the maximum score. The test administration normally takes from 5 to 15 minutes.

The *Theory of Mind Picture Sequencing Task* (PST) is a test developed by Brüne [46] to assess the relation between intelligence and ToM abilities in schizophrenia. During this test the patient is asked to put in the right sequence some vignettes that describe a story. There are 6 stories, each one consists of 4 pictures to be put in order by the patient in a logical sequence as fast as possible. Two stories describe a scenario were two characters cooperate, other two stories describe a scenario where one character deceives a second character; the last two stories describe a scenario where two characters cooperate to deceive a third. For example in the story of the apple tree, there is a boy who is trying to get an apple from a tree, while another boy is reading, the first boy cannot get the apple and asks the second to help him, they manage to get the apple and in the last picture they eat it together. Then the examiner makes some questions to evaluate the patient's ability to infer the mental states of each character of the stories; questions will concern levels of understanding, levels of growing complexity, first and second order false belief; tasks about cheating detection and questions about reality. For example, about the apple tree story, it is asked "What does the person with the red shirt believe the one in blue shirt intends to do?" to evaluate the second order beliefs, or " What does the person with the red shirt expect from the person in the blue shirt?" to evaluate the patient's ability to understand the reciprocity in the scene. If subjects fail to put in the right order the stories, the examiner will put the pictures into the correct order before making other questions. For the correct order of the pictures and for the answers, will be given a score whose maximum value is 59 points.

The *Irony task* [51] is a test that consists of 63 vignettes: 31 pictures where it is necessary to ascribe ignorance, false belief or deception to one of the character, thus analysing his/her mental state in order to understand

TABLE I.
Mean and standard deviation of the three groups. *Media e deviazione standard dei tre gruppi*.

	CONTROL		ONSET		CHRONIC	
	Mean	SD	Mean	SD	Mean	SD
Age	29.22	6.77	23.57	2.27	34.14	5.17
Hinting	19.61	0.50	17.57	2.56	13.21	5.11
PST P	57.61	2.03	51.00	6.59	42.86	10.57
PST T	119.5	26.96	209.21	94.00	257.21	72.2
Irony P	23.22	2.92	19.00	8.19	11.21	6.85
Irony T	460.11	128.86	663.57	344.31	866.79	225.53
Irony H	2.16	0.45	2.66	0.59	3.63	0.22
Irony D	1.95	0.42	2.12	0.56	2.67	0.69
Eyes test	28.5	2.68	24.57	3.95	21.5	5.41

Hinting: Hinting Task Total score; PST P: Theory of Mind Picture Sequencing Task Total score; PST T: Theory of Mind Picture Sequencing Task Total time; Irony P: Irony Task Total score; Irony T: Irony Task Total score; Irony H: Irony Task Degree of fun; Irony D: Irony Task Degree of difficulty; Eyes Test: *Reading the Mind in the Eyes* Total score.

irony (ToM vignettes). The remaining 32 vignettes describe physical events or behaviours that do not need ToM abilities to be correctly understood. Subjects are requested to observe each vignette and to indicate to the examiner its meaning as soon as they will understand it. Later the subjects give their own brief explanation of the meaning of the vignette itself. The examiner records with a timer the time the subject needs to explain the vignette. If the explanation is correct 1 point is given, 0 points if is incorrect. The explanation is considered correct only if a suitable mental state is ascribed to one or more characters. An objective score is obtained from the total of the correct answers. It is also requested to give a subjective score (from 1 to 5) about the degree of fun and the degree of difficulty to understand each vignette. We chose 30 of the 63 humorous vignettes (15 ToM + 15 Physical) in order to shorten the times of test administration.

The *Reading the Mind in the Eyes* or *Adult Eyes Test* [48] is a test that considers the eyes as the part of the face mainly involved in expressing complex emotions. In this test are shown 36 pictures with different set of eyes, to each set of eyes are ascribed 4 adjectives and the subject has to choose the one that best describes what the person in the picture is thinking or feeling. This test was useful to understand and evaluate the subject ability to put himself in the other's mind, tuning in with his/her mental state.

The *Beck Cognitive Insight Scale* [52] evaluates patients' self-reflectiveness according to their experiences, the self-certainty and the ability to self-correct their own wrong judgements. It consists of a 15-item self-report questionnaire, divided into two sub-scales. The first subscale consists of 9 items about self-reflectiveness, it evaluates subject's objectivity, reflectiveness and openness to feedback. The second sub-scale instead consists of 6 items measuring decision making, high degree of certainty in one's interpretations: for example it assesses the "Jumping to conclusions", certainty of being right and resistance to corrections. The subject is asked to give an answer to each question on a 4-point scale, from 0 (do not agree at all) to 3 (agree completely). The test had no time limit. Detracting the second sub-scale from the first one, we have a composite index, the BCIS, that reflects the degree of the cognitive insight, in other words the introspective ability and the capacity to understand one's own errors.

An example of clinic application

In order to evaluate the sensitivity and specificity feature of the battery of tests, we have administered the different tests to two groups, each one composed of 15 patients of the DSM clinics of the ASL RMD; they were all diagnosed within the schizophrenia spectrum, diagnosis made according to DSM IV-TR criteria by psychiatrists specialized in the treatment of such diseases. The first group was composed of young patients at their first crisis, with less than 3-5 years of disease (mean age: 23 years old); the second group of chronic patients with more than 5 years of disease (mean age: 34 years old). Such partition was made according to Birchwood's hypothesis, who identified in the first 3-5 years of disease the so called "critical period", when the main social and personal impairments are developed, with the resulting loss of self-esteem, relationships and competence at school and at work. The tested patients are all males, except for one girl of the first group. All of them, at the moment of the test, were in stable clinical conditions and benefited of the same services offered by the ASL RMD, including pharmacological, clinical, and rehabilitative treatment. Patients with mental retard, cranial trauma, neurological disorders, epilepsy, substance misuse at the moment and for more than 6 months, were excluded. The outcomes for both the clinical groups were compared to those of a control group composed of 15 healthy male subjects, all the selected tests were administered to them.

The aim is to evaluate the quality of the battery, to understand the differences in ToM ability according to a heterogeneous population like the schizophrenic one, that shows an impairment in such skill. These ToM impairments indeed are already present in the subjects at their very first episode and tend to become more serious and pervasive during the years, damaging in this way the social functioning.

At a first examination of the mean and standard deviations of the scores resulting from the several tests it appears clear the general tendency to impairment for both the samples; if we compare them with the results obtained from the test previously administered to a sample of healthy subjects with an age that ranges from 20 to 40, we can see that the clinical samples have worse scores compared to the healthy ones, and at the same time, they need more time to carry out the tasks, if we consider for example the time measurement for *Brüne*'s and Irony tests. It seems that patients try to balance their performance (that is still problematic) taking more time to give an answer.

Later on, we have evaluated the significance of differences between the performance made by the subjects of the clinical samples using the one way ANOVA with the Tukey Post hoc test and with significance < 0.05 (Tab. II). From the data obtained it appears as the worst functioning in chronic patients compared to the control group, is more significant in all the tests that have been administered, contrary to what happens in the early onset group, where there were no significant differences in the Hint-

TABLE II.
Turkey Post Hoc. *Turkey Post Hoc*.

Variabile	Sample (I)	Sample (J)	Mean Difference (I-J)	Sig
Hinting	Control	Onset	2.040	.178
		Chronic	6.397	.000
	Onset	Chronic	4.357	.002
PST T	Control	Onset	-89.714	.002
		Chronic	-137.714	.000
	Onset	Chronic	-48.00	.155
PST P	Control	Onset	6.611	.029
		Chronic	14.754	.000
	Onset	Chronic	8.143	.010
Irony P	Control	Onset	4.22	.144
		Chronic	12.008	.000
	Onset	Chronic	7.786	.005
Irony D	Control	Onset	-.167	.680
		Chronic	-.725	.002
	Onset	Chronic	-.557	.031
Irony H	Control	Onset	-.495	.010
		Chronic	-1.038	.000
	Onset	Chronic	-5.428	.008
Eyes test	Control	Onset	3.929	.025
		Chronic	7.000	.000
	Onset	Chronic	3.071	.124

Hinting: Hinting Task Total score; PST P: Theory of Mind Picture Sequencing Task Total score; PST T: Theory of Mind Picture Sequencing Task Total time; Irony P: Irony Task Total score; Irony T: Irony Task Total score; Irony H: Irony Task Degree of fun; Irony D: Irony Task Degree of difficulty; Eyes Test: *Reading the Mind in the Eyes* Total score.

ing and in the Irony test. The different seriousness of ToM abilities impairment for the two clinical samples appears even if we compare them; effectively there were statistically significant differences in *Brüne*, Irony (except for the time) and Hinting tests.

Discussion

There is widespread agreement in literature, about the central role played by the metacognitive deficit in causing the social functioning impairment in serious psychiatric disorders particularly in schizophrenia [3,4]. Patients diagnosed within the schizophrenia spectrum show an overall deficit of metacognitive functions [1,2,5]. These observations call for the need to integrate in the assessment routine of such patients a specific protocol of evaluation for this area. In this study we have presented a battery of tests that has to evaluate the metacognitive functioning of these patients using a multi dimensional perspective; only the use of different tools allows to understand and measure the multi dimensional complexity of such functions [5,8].

The implementation of this battery have highlighted the presence of metacognition impairments since the early years of the disease, the comparison between the chronic patients and others at the early onset, showed a gradual impairment of such abilities. The differences between the group of chronic and the subjects at the early onset of the disease, are indeed significant, except for the Eye test and for the times obtained in the Irony test. The outcomes can be surely generalized, because of the small number of subjects of the different groups, but they allow us to make some hypothesis for this pilot study:

- it is necessary to evaluate the metacognitive functions through a wide battery of tests, contrary to what many studies carried out until now; tasks that consider the different aspects of metacognition, not only the specific ToM ability;

- instead of classifying metacognitive dysfunctions simply as present or absent, as state or trait markers, it could be more interesting and therapeutically significant to evaluate the gradual impairment, keeping in mind that some metacognitive areas could be impaired at the beginning but not yet significantly altered.

The proposed battery, besides showing a good sensitivity in noticing the presence of an impairment, it also answers to the need to evaluate metacognition under a multidimensional perspective. Both the social cognitive tasks (that analyse the ability to understand the mental states of others) and the social perceptual tasks (that evaluate the implicit mental states decoding) were adopted; and a classic test "paper and pencil" has been added as a self-report questionnaire.

With the *Theory of Mind Picture Sequencing Task* (that is a task about false belief and deception) some vignettes are used to infer false beliefs belonging to one of the character of the story and the false beliefs of one character about the mental state of another. Tests like the *Irony task* and the *Hinting Task*, instead assess the pragmatic skill of the patient, in other words the ability of going beyond the literal meaning of words to infer and evaluate the speaker's beliefs and communicative intentions, even in a conversational context. Among the "social perceptual" tests there is the *Reading the Mind in the Eyes* that allows to infer mental states from the visual expression, using both the theory of mind abilities and the identification of the most basic emotions. We considered only a self-report tool, the *Beck Cognitive Insight Scale*, that evaluates the subjects' self-reflectiveness.

The decision to use tests that assess the different functions, using different types of tasks, allow to reduce, at least in part, what we consider to be the main limit of the battery, in other words these are evaluations carried out in "clinic", in an environment that is not emotionally stimulating. In a future perspective we would like to integrate tools that can give suggestions about the patients' capacity to "mentalize in the field"; even patients that seem to be capable, when they are evaluated with specific testing assessment, can show difficulties in metacognitive functioning, such difficulties make them less efficient and less fast when they have to interact in the dynamic structure of everyday life.

Conflict of interests

The authors declare that there are no conflicts of interest. The authors have not received grants.

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When economic theory meets the mind: neuroeconomics as a new approach to psychopathology

Quando la teoria economica incontra la mente: la neuroeconomia come nuovo approccio alla psicopatologia

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Summary

The paper describes the current status of the new interdisciplinary research field of neuroeconomics in relation to psychopathology, giving an account of possible clinical implications for social dysfunction. This is achievable because neuroeconomics join economics, psychology, neuroscience and computational science in order to gain a greater understanding of people decision making. Recent research are using these tasks in association with neuroimaging in order to understand existing discrepancy between the theoretical models and experimental data and to gain more details on the ways people decide and judge within the social context. We report how neuroeconomics paradigms have been recently used to study social interaction in different mental disease conditions such as in borderline personality disorder, externalizing behavior problems, depression, social anxiety, psychopathy, autism and, more recently, psychosis.

Furthermore the paper aims to point out a new set of tools from Economics Theory able to gather human interaction 'in vivo' in a computable way. The challenge of neuroeconomics may be to bring a broad set of tools letting new knowledge on neural computation of social interaction and, extensively, on mental diseases where the social impairment is a core feature.

In conclusion the paper speculates that neuroeconomics is a potential bridge for translational research in psychopathology as it allows to get an objective evaluation of the interpersonal behaviors in a shifting social environment and to combine behavioral with neuroimaging measures, as tools to investigate relationship between neurobiology and behavior.

Key words

Neuroeconomics • Decision making • Psychopathology

Neuroeconomic basis of decision making: from economic theories to real world choices

Neuroeconomics is a new interdisciplinary research field which combines economics, psychology, neurosciences and computational science in order to gain a greater understanding of people decision making (DM). The study of DM has received significant attention from economists and psychologists in the last few decades. These studies provided both cognitive accounts of preferences as well as understanding of the ways in which neural processes mediate risk-taking behaviour that model real-life choices [1].

This emerging discipline is able to connect computational theories, in particular the reinforcement learning, and game theoretical approach to elements of neural circuits underlying social DM variables. Neuroeconomics may offer a broad theory of human behaviour to study learning, social exchange and cooperation, brain reward pathways and neurotransmitter systems, connecting sensations and actions, disclosing their neurobiological substrates [2 3].

If so, neuroeconomics provides a new approach with new experimental paradigms and tools borrowed from economics science supporting the social neuroscience research in its continuous challenge to find the underlying mechanisms responsible for social behaviour. In the real world the ability to understand others' minds and intentions and beliefs (Theory of Mind – ToM), socially relevant stimuli, make interpretations about their meaning and behave according to decisions that are accurate, optimal and adaptive, are essential to successfully navigate ourselves through the social context. In so far, neuroeconomics may turn in an intriguing tool to ascertain the 'social predicting brain' in the more disparate contexts of DM within human interactions [2].

Traditionally, choice behaviours were studied within economic models according to the global DM theories of 'Utility', the ability of the individual to satisfy needs or wants, criterion of the best option and measure of satisfaction. If economists have devised ways of representing and measuring 'Utility' in terms of economic choices that can

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be counted, this computation is not easy in social decision context, in which one needs to infer the probabilities and values of the partner or opponent in attempting to reach the best decision to obtain satisfaction. This aim can be reached by new tools derived from emerging neuroeconomics paradigm.
In a similar way Economics applies Utility Theory, Neuroeconomics uses the mathematical Game Theory giving the opportunity to apply specific models to social exchange exploration. Game Theory aims to capture rational decisions and choice behaviour in simulated social situations. The essence of Game Theory is strategic interpersonal reasoning: in a two player game, one agent chooses among the range of possible moves depending upon the decision of the Second Agent. The Primary Agent has to form mental models regarding what the Second Agent will do based on his prospective or predicted moves and payoffs.
Neuroeconomics uses Game Theory to investigate cooperation, reciprocity, fairness, and altruism as illustrated by the famous games known as the Trust Game and Prisoner's Dilemma Game (PDG) [4 5]. In the former game the player (Investor) decides to invest money through a partner (Trustee) and during the transfer the amount is multiplied by some factors, so that the Trustee may return some, all or any money. Essentially the game is based on trust: if the Trustee respects trust reciprocating money, both players end up with higher payoff. The PDG is a similar paradigm, but both players choose to cooperate or not simultaneously, without knowing what the partner will chose to do. Game Theory predicts that in the former game, if the players consider each single interaction during the game, a *purely* rational Trustee will never reciprocate trust received and the rational Investor, realizing this, should invest zero in the transaction and, in the latter, players immediately will fail to mutual defection. What is further interesting from our perspective is that, despite these rational predictions, most of people playing are more trustfully, cooperative and less selfish than expected.
Another interesting set of tasks derived from Game Theory is bargaining games, in particular The Dictator and Ultimatum Games used to study behaviours of equality and inequality. In the former one player (Proposer) decides how much offer to the other player (Responder), in the second game the players need to divide a sum of money in order to both have a payoff, with the Proposal deciding the amount and the Responder accepting or not the offer: in case of rejection both players gain zero. According to the rational prediction the Responder should accept any offer and the Proposer should offer the smallest amount possible.
Again, differently from theoretical predictions, observed behaviours show that low offers than 20% of the total amount are rejected about half of the time, underlining a trend to altruistic punishment where the Responder prefers to get no money rather than a miserable offer.
Recent research are using these tasks in association with neuroimaging in order to understand this discrepancy between the theoretical models and experimental data and to gain more details on the ways people decide and judge within the social context.

How psychopathology is using neuroeconomics

Economic theories allow to study different interacting factors in the framework of a single model taking into account motivational drives. This feature is of interest for disciplines as psychiatry and clinical psychology that need real world approaches to study the interplay of social, psychological and biological factors underlying psychopathology.
By varying task characteristics (e.g., strategies, payoffs, and structural features of interactions, such as context and communication between players), simple games can be adapted to probe a remarkable range of social phenomena, including social influence, prosocial behaviour, trust, social-norm violations, social-cognitive biases, group dynamics, and higher-order social cognition [6 7].
Neuroeconomic paradigms have been recently used to study social interaction in different mental disease conditions: borderline personality disorder (BPD), externalizing behaviour problems, depression, social anxiety, psychopathy, autism and, more recently, psychosis.
King-Casas et al. [8] used the iterated version of the Trust task to examine trust in adults with BPD. When cooperation began to falter in the iterated interactions but cooperation is hoped, BPD subjects showed an insensitivity of anterior insular cortex in comparison to healthy subjects. A similar result was achieved by Unoka et al. [9] who found that decreased trust was specific to borderline patients, as opposed to depressed patients, exclusively when the risk -taking is social. These results can be ascribed to an abnormal social input perception in BPD.
Sharp et al. [10] instead used the trust game under the two conditions of anonymous and known-identity to study externalizing behaviour problems in adolescence. Prior social and moral information about partners (i.e., reputations) modulated reward responses in the adolescent brain, where a reduced reciprocity was shown during social reasoning independently from ToM functioning. These results are in line with findings from studies with adults [11].
Monterosso et al. [12] provided evidences in the addiction area studying how people value the near-term and medium-term future in relation to prediction-error signalling and the connected neural substrates.
Ernst [13] reviewed reward-related and goal-directed pro-

cessing in relation to symptoms of depression providing a possible map and connection of the DM processing to neural dysfunction. In the context of social anxiety the major result reported diminished activity for social than to nonsocial partners (i.e. a computer) in a region of medial PFC implicated in ToM.
Findings from a study on psychopaths showed that different patterns of activity in brain areas associated with social emotion regulation (e.g., the dorsolateral prefrontal cortex) were achieved during Prisoner's Dilemma (PD) game with high non-cooperative responses [14]. A general tendency to competitive behaviours, non fairness and exploitation of partners in criminal psychopaths [15] and a comparable level of non-cooperation in psychopaths to those of patients with frontal-cortex lesions as investigated by the Dictator Game [16] were also observed.
Fett et al. [17] using Trust Game showed that patients with psychosis and healthy relatives with a heightened risk for the illness exhibit lower baseline levels of trust compared to healthy controls.
In autism a study using Dictator Game, showed a specific insensitivity to social reputation of autistic subjects when observed by others during charity donation.
All these results demonstrated a validity of neuroeconomics tools, with their specific adaptations to each context, to investigate and discriminate psychiatric disorders.

Neuroeconomics for the social exchange real-world discovery

Why this kind of computational approaches are of interest for psychopathology?
The answer rises from the gap existing in psychology and in psychiatry due to a lack of adequate intermediate levels of description between the neural level and the phenotype, such as mental illness. This is especially true for the understanding of social behaviour impairments specific of some disorders, such as schizophrenia.
The neuroeconomics approach may be relevant for the study of interpersonal dysfunction in psychiatric diseases, where a biological understanding has been achievable only in recent decades, due to the great difficulty in quantifying and parameterizing social cues. Indeed economic games provide the cognitive science with tools of new ecological validity, studying the interaction *in vivo* rather than through static stimuli as face, stories, cartoon comprehension or reasoning and judging about hypothetical scenarios.
The challenge of neuroeconomics may be to bring a broad set of tools letting new knowledge on neural computation of social interaction and, extensively, on mental diseases where the social impairment is a core feature.
The point is that to understand the neurobiology of social dysfunction, one must measure neural activity when participants engage in social interaction or make social decisions. Neuroimaging allows to face this challenge by 'hyperscanning' technology that may image brain functions during partners interaction, simultaneously, using network connections between two separate scanners. Two other interesting methods involves the manipulation of specific neurotransmitter systems with the examination of consequent effects on game-playing behaviour and the use of transcranial magnetic stimulation to activate and disactivate specific brain regions, with the aim to examine the effects on social decision making [18].
However social interaction and psychiatric illness are difficult to assess because of the vast state space of social behaviours and the few external indicators of psychopathology beyond self-report and symptoms ascertained through clinical interviews or behavioural observation to aid in objective psychiatric diagnosis [6 19]. Multiplayer economic games provide a tool to evoke, monitor and measure the degree and type of social impairment in distinct psychiatric illnesses.

Conclusion remarks and future directions

Neuroeconomics approach offers an exciting chance for computing and quantifying social cues allowing a more extensive measurement of interpersonal dysfunction in mental diseases. It is a potential bridge for translational research in psychopathology as it allows to get an objective evaluation of the interpersonal behaviours in a shifting social environment and to combine behavioural with neuroimaging–measures, as tools to investigate relationship between neurobiology and behaviour. Further it permits the development of a common language among the multilevel research paradigms from economics, neurosciences, psychology and psychiatry disciplines to investigate social DM in mental diseases. If so neuroeconomics may be also useful for the study of possible endophenotypes.
Moreover it is important to underline that in any way this approach aims to supplant existing nosologies. Although these models are still quite simple and need many changes to work well in the complexity of human interactions, they may represent an useful add-on for further interpretation of mental functions. So far, evidences from studies on mental disorders using neuroeconomics are encouraging.
Future research may deepen social interaction investigation especially when interpersonal dysfunction is a core feature. This may be achieved for he social difficulties of mood and anxiety disorders that may lie in social probability distortion that prejudice social learning and disrupt social functioning (e.g., social anhedonia). Multi-agent game theoretic paradigms that vary the probability and valence of specific interpersonal gestures may be a useful starting point from which these issues can be examined

and validated. The investigation through neuroeconomics paradigms could be of interest also for the study of vulnerability and resilience to peers influence for risk-taking behaviours in adolescence groups.
Within this framework social valuation (i.e., how much does one value specific social gestures), social risk preferences (i.e., how sensitive is one to social uncertainty), and social inference (i.e., how competent is one at inferring the intentions of social others) may provide unique discriminating vectors among distinct psychopathologies [6].
As social anhedonia seen in depression may signal diminished value from social interactions (whereas susceptibility to peer influence may signal excessive value), the fear of embarrassment in social anxiety may reflect impaired social risk assessment, and in autism, impairments in social inference may manifest as a lack of social reciprocity. Of interest is also the possibility to investigate subtypes of psychotic experiences, such as paranoia using a trust paradigm [20].
Finally, interactive games from economics theories joined to neuroimaging and computational learning theory, provide a paradigm that can be used to study the underlying neurobiology and genetic correlates of social behaviour. They can help in differentiate diagnostic categories or assess criteria, provide bio-behavioural targets for novel strategies treatment of interpersonal difficulties, bridging in some way the existing gap between neurobiology and behaviour.

Conflict of interests
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Catatonia from the first descriptions to DSM 5

Catatonia dalle prime descrizioni al DSM 5

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Summary

Aims

This paper aims to provide an update to clinicians regarding the changes of the diagnostic criteria of catatonia in DSM 5.

Methods

The authors have made a review of the literature concerning catatonia using the keywords mentioned below; the various versions of DSM have been also consulted.

Results

Although catatonia has historically been associated with schizophrenia, it occurs more frequently in conjunction with mood disorders or somatic diseases.
Therefore, since the fourth edition of the DSM, catatonia has been both a specifier for affective episodes and it has been possible to make diagnosis of catatonia due to a general medical condition.
In DSM 5 four changes have been made: 1) the catatonia is described in the whole manual, regardless of the condition which appears to be associated with, by the same type and number of criteria, 2) it is a specifier both of schizophrenia and affective episodes (the catatonic subtype of schizophrenia has been removed), 3) it is used as a specifier for other psychotic spectrum disorders, and 4) finally, there is the category "NOS" that allows the rapid diagnosis where the etiology is not immediately identifiable.

Discussion

These changes will improve the recognition of catatonia within the various psychiatric disorders and they will facilitate the treatment.

Key words

DSM • Catatonia • Mood disorders • Schizophrenia • Diagnosis

Introduction

In 1874 Karl Kahlbaum described catatonia as an independent psychiatric syndrome characterized by cyclic course and alternating manic, depressive and psychotic phases, with an eventual deteriorative course [1]. In the early years of the twentieth century Emil Kraepelin described catatonia as a possible manifestation of *dementia praecox* [2]. Bleuler, following Kraepelin's approach, categorized catatonia as a subtype of schizophrenia [3]. In the subsequent years, the term "catatonia" was considered a synonymous of schizophrenia. This diagnostic classification prevailed in the scientific literature of the twentieth century, conditioning the first editions of the ICD and of the DSM classifications [4-9].

Catatonia in the diagnostic classification systems

During the 80s and 90s a number of studies suggested that catatonic syndromes could complicate the course not only of schizophrenia but also of affective disorder and different medical conditions, such as metabolic (renal or liver failure, ketoacidosis, vitamin B12 deficiency), endocrine (hyperthyroidism, hypercalcemia from parathyroid adenoma, Addison's disease, Cushing's disease, SIADH), neurological (encephalitis, multiple sclerosis, epilepsy), rheumatologic (systemic lupus erythematosus) and infectious diseases (typhoid fever, mononucleosis, malaria) [10-12 13-18].

For these reasons the authors of the last versions of the most important diagnostic classification systems changed their approach to catatonia.

In particular the International Classification of Disease (ICD-10) [9] added the possibility to diagnose an "organic catatonic disorder" while the DSM-IV [7] enlarged the borders of catatonia to three different contexts:

1. Catatonic Disorder due to a General Medical Condition;
2. Schizophrenia-Catatonic Subtype;
3. Episode Specifier for Major Mood Disorders without specific numerical code (Bipolar I disorder – *single manic episode; most recent episode manic; most recent episode depressed; most recent episode mixed* – or Major Depressive Disorder – *single episode or recurrent*).

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The clinical picture of catatonia in DSM IV is characterized by five groups of symptoms (Table I).
The manual requires the presence of at least two of the five groups of symptoms for the diagnosis of catatonia as a subtype of schizophrenia or as a specifier of an affective episode, while for the diagnosis of "catatonia due to a general medical condition" is sufficient the observation of only one of the five sets of symptoms.
Even if DSM IV represented an important step towards the recognition and assessment of catatonia, some authors criticized this approach:

1. DSM IV criteria remain vague, leading to a discrepancy between the frequent clinical observation of catatonic symptoms in patients with psychiatric (7-31% of cases) or somatic disorders (20-25 % of cases) [15 16 19-21] and the relative rarity of the diagnosis of catatonia [22]. Even the diagnosis of catatonic schizophrenia is rarely used (0.2-3% of all diagnoses of schizophrenia) [23 24];
2. catatonic schizophrenia, as formulated in the DSM-IV, is of low clinical utility, penalized by a low stability and poor reliability [25-27]. Van der Heijden et al., (2005) found that among patients admitted with acute psychosis catatonic symptoms were recognized in 18% of the sample when assessed by skilled clinicians and in only in 2% when assessed by clinical practitioners [21];
3. according to DSM-IV catatonia can be diagnosed only in the context of schizophrenia (as subtype) or major mood disorders (as an episode specifier) [7]. Actually catatonia is also present in other psychiatric disorders. Individual case reports and extensive clinical case series report the presence of catatonia in the context of schizoaffective, schizophreniform, brief psychotic disorder, substance-induced psychotic disorder [28-30], obsessive-compulsive disorder, autism and other developmental disorders [31-35];
4. the manual did not permit a diagnosis when the link between catatonia and a medical/neurological disorder is not immediately evident, as it happens in the initial stages of a clinical evaluation. Clinical experience and research data have highlighted the importance of early diagnosis of catatonia, especially for the therapeutic-prognostic implications [36-39]. The term of "idiopathic catatonia" is often used in these cases [40 41], even if it is not recognized neither in ICD-10, nor in the DSM-IV.

TABLE I.
Diagnostic criteria for catatonia in DSM-IV (APA, 1994). *I criteri diagnostici per catatonia nel DSM-IV (APA, 1994).*

At least one (Catatonia secondary to a general medical condition)/two (for Catatonia subtype of schizophrenia/specifier of mood disorder) of the following:
1. Motor immobility as evidenced by catalepsy (including waxy flexibility) or stupor
2. Excessive motor activity (that is apparently purposeless and not influenced by external stimuli)
3. Extreme negativism (resistance seemingly no reason at all commands or maintenance of a rigid posture against attempts to be moved) or mutism
4. Peculiarities of voluntary movement as evidenced by the trend towards fixed posture (voluntary assumption of inappropriate or bizarre postures), stereotyped movements, mannerisms or prominents grimacing
5. Echolalia or echopraxia

Catatonia as an autonomous diagnostic category

According to some authors the most important limit of DSM-IV approach is that catatonia is not recognized as a specific syndrome [42]. The hypothesis that catatonia should be considered an autonomous diagnostic category is based on some clinical evidences:

a. catatonia is common, though not always correctly recognized. In the 10 principal prospective studies from 1990 to 2010, catatonia was identified in a mean percentage of 9.8% of adult admission. These patients have multiple signs of catatonia (commonly >5); 68% are mute and negativistic and 62% are withdrawn. Some are unable to eat, requiring parental nutrition and/or medication [42];
b. catatonia syndrome is identifiable, characterized by a well defined clinical picture although it occurs with extremely variable signs and symptoms. Several Catatonia Rating Scales, as the Bush-Francis Catatonia Rating Scale [43], can help in identifying catatonic symptoms. Factor analytic studies have delineated patterns among catatonic features. In particular, Taylor and Fink have extracted two factors: one consisting of catalepsy, posturing, mutism and negativism and a second characterized by echophenomena, automatic obedience, verbigeration and other stereotypies [44];
c. catatonia has a stable course, described by various researchers as a generally cyclic disorder, with episodes of excitement, depression and psychosis. The course is not malignant, as described in the past: the good response to specific treatments in most cases prevents the worse outcome;
d. catatonia is frequently associated with mood disorders. Considering catatonia as an independent syndrome would definitely separate the diagnosis from schizophrenia [45 46]. Only 10-15 % of catatonic patients present a diagnosis of schizophrenia and, according to recent data, the frequency would be even lower

(7.6%) [47]. Catatonic episodes are most frequently associated with mood disorders, particularly with severe form of mania. About one third of patients who accesses mental health services with catatonic features presents bipolar disorder. Patients with bipolar disorder and catatonic symptoms present a higher number of mixed episodes, greater severity of manic symptoms, and longer periods of hospitalization. Finally, catatonia usually has a poor response to antipsychotics (7.5%), which sometimes may also complicate the clinical picture, facilitating the development of the malignant form [37];

e. catatonia has a specific diagnostic test: the lorazepam challenge test consists in an intravenous injection of 1 mg of lorazepam. If no change is observed over a period of 5 minutes, an additional dose of 1 mg is injected i.v. Within 10 minutes, in at least two-thirds of patients there is a reduction in stiffness, the appearance of spontaneous movements and recovery of speech. The positivity of the test encourages the use of intravenous lorazepam, in doses ranging up to 24 mg/day, with a satisfactory response in 90% of cases. The negativity does not rule out a possible subsequent therapeutic response to BDZ, but suggests the preferential treatment with ECT [45];

f. once diagnosed, catatonia responds to specific treatments (Table II). Unfortunately, the correlation with schizophrenia, has prompted the use, potentially harmful, of antipsychotics. On the other hand, if not immediately recognized, catatonia may be complicated by severe somatic diseases such as malnutrition, infection, muscle contractures, bed sores, and thrombo-embolism;

g. catatonia has neurobiological specific correlates: many authors suggested a correlation between catatonic symptoms and specific alterations of the striatal-thalamic-cortical circuit, involving the frontal and parietal cortex, the basal ganglia and cerebellum [44 48]. The efficacy of BDZ seems to suggest an impairment of the GABAergic system; indeed, some authors reported a reduction of GABAergic function and blood perfusion in the right lateral orbitofrontal cortex in patients with catatonia. Since this area has direct connections with the amygdala, its involvement may explain the intense feelings of fear and anxiety often reported by catatonic patients. The GABAergic system also exerts a tonic inhibition of circuits that regulate innate behavioral sequences: a reduction of the GABAergic activity in these areas may results in the reappearance of predetermined behaviors towards stressful situations. These manifestations could also be the consequence of a hyperactivity of glutamatergic circuits, which would lead to a dysfunction of the posterior parietal lobe responsible for the trunk with the prefrontal cortex, which would justify the appearance of symptoms such as posturing and alteration of the position of the body segments in space, with a possible rationale for the use of antagonists of NMDA receptors [49 50]. Finally, the dopaminergic circuit is modulated by the GABAergic system and serotonergic projections from the dorsal raphe: the alteration of dopaminergic transmission would compromise the thalamocortical circuit. For these reasons Northoff et al. [51] have recently suggested that catatonic syndromes are sustained by an impairment of the GABAergic system with a secondary involvement of the dopaminergic transmission responsible for the movement disorders ("top-down dysregulation").

TABLE II.
The treatment of catatonia. *Il trattamento della catatonia*.

BDZ i.v. (in particular lorazepam): especially effective when the challenge test is positive; dosages must be high and the treatment should be prolonged until complete resolution of catatonic symptoms. In these cases the overall response rates is around 70%
ECT: is effective in about 85% of cases, and represent the treatment of choice in the malignant form (about 90% of these have a positive response to ECT and only 40% to BDZ) or in the excited-delirious form of catatonia. Sessions of ECT should be rather close (typically three per week)
BDZ i.v. + ECT: can be used together, given their synergic effect, even if the dose of benzodiazepines should be reduced as they can rise the seizure threshold.
GABA-A agonist zolpidem and NMDA antagonists (memantine, amantadine): few positive data.
Antiepileptics: their use is still doubtful, but certainly not harmful

Among the main supporters of a "catatonic syndrome", Taylor and Fink, coming back to the unitary point of view of Kahlbaum [18 36 44 52], proposed to consider catatonia as an independent diagnostic category (similar to what happened for the *delirium*), characterized by a unique numeric code and represented by three clinical subtypes:

- nonmalignant catatonia (*Kahlbaum syndrome*): the most frequent form of catatonia, characterized by immobility, mutism, negativism, posturing, rigidity up to stupor. This clinical picture has a positive response to treatment with benzodiazepines (lorazepam generally, 6-20 mg intravenously);
- delirious catatonia: defined by the presence of excitement, aimless hyperactivity, stereotypies, verbigeration, altered state of consciousness and delirium. It requires high doses of benzodiazepines, usually worse

if treated with antipsychotics (possible evolution in the malignant form) and often requires the adjunctive use of ECT;

- malignant catatonia: characterized by acute onset, fever and evidence of autonomic instability (hypo/hypertension, tachycardia, tachypnea, diaphoresis), increased enzyme of muscle necrosis, reduction of circulating iron, leukocytosis. Somatic complications are frequent (dehydration, infections, thromboembolic phenomena). It requires life-supportive care and it is potentially fatal if not promptly and adequately treated. This form usually respond to ECT, while response to benzodiazepine is poor or inconsistent. The authors included in this group also the Neuroleptic Malignant Syndrome and the Serotonin Syndrome [44].

For each of these clinical subtypes the authors suggested four specifiers: a) secondary to mood disorder; b) secondary to a general medical condition or toxic state; c) secondary to a neurological disorder, d) secondary to a psychotic disorder.

Fink and Taylor, moreover, suggested a set of different diagnostic criteria for catatonia (Table III) to address the poor specificity of DSM-IV diagnosis. First of all they criticized the fact that, according to DSM-IV criteria, the non-specific features of immobility and excitement are sorted equally with the more specific features of catalepsy, waxy flexibility, negativism and mutism. While catalepsy and echophenomena are specific catatonic features, excessive motor activity and severe immobility are not. Then, the authors have underlined the absence of a duration criterion, which compromises diagnostic reliability. Catatonic features typically come and go and can be quite variable in time: Fink and Taylor stressed the need that symptoms last at least one hour in order to facilitate reliability among observers. The authors tried to strengthen the boundaries of the syndrome, to facilitate further study and the application of appropriate treatments.

TABLE III.
Fink and Taylor's recommended diagnostic criteria for catatonia (adapted from Fink and Taylor, 2003) [13]. *I criteri diagnostici di Fink e Taylor raccomandati per la catatonia (adattato da Fink e Taylor, 2003)* [13].

A. Immobility, mutism, or stupor of at least one hour duration, associated with at least one of the following: catalepsy, automatic obedience, posturing, observed or elicited on two or more occasions
B. In the absence of immobility, mutism or stupor, at least two of the following, which can be observed or elicited on two or more occasions: stereotypy, echophenomena, catalepsy, automatic obedience, posturing, negativism, ambitendency

DSM 5

The authors of the DSM 5 considered all the hypotheses and suggestions proposed in the field of catatonia during the last two decades and obviously decided to take into account only some of them. A great effort was spent to improve the usefulness and applicability of the clinical diagnosis of catatonia. Compared to the previous version of the manual, the DSM 5 introduces four key changes (Tables IV-V):

a. criteria for catatonia are the same throughout the manual, independent from the initial diagnosis: psychotic, bipolar, depressive, medical disorders or an unidentified medical condition. In order to facilitate the recognition, catatonia is defined by the presence of at least 3 symptoms from a list of 12, extracted from a validated rating scale by Peralta et al. [53 54] (Table IV);

b. the catatonic subtype of schizophrenia is deleted (along with all other schizophrenia subtypes) and catatonia becomes a specifier for schizophrenia as for major mood disorders;

c. catatonia becomes a *specifier* for four additional psychotic disorders: 1. Brief psychotic disorder; 2. Schizo-

TABLE IV.
Definition of catatonia in DSM 5 (APA, 2013). *Definizione della catatonia nel DSM 5 (APA 2013).*

Catatonia is defined by the presence of three or more of the following:
1. Catalepsy (i.e., passive induction of postures held against the gravity)
2. Waxy flexibility (i.e., slight and even resistance to repositioning by the examiner)
3. Stupor (no psychomotor activity, no reactivity to the environment)
4. Agitation, not influenced by external stimuli
5. Mutism (i.e., no or minimal verbal response- not applicable in case of established aphasia)
6. Negativism (i.e., opposing or not responding to external stimuli or instructions)
7. Posturing (i.e., spontaneous and active maintenance of posture against gravity)
8. Mannerism (i.e., odd caricatures of ordinary actions)
9. Stereotypies (i.e., repetitive, frequent, non-goal directed movements)
10. Grimacing
11. Echolalia (i.e., repeating the words spoken by the examiner)
12. Echopraxia (i.e., mimicking of movements made by the examiner)

phreniform disorder; 3. Schizoaffective disorder; 4. Substance-induced psychotic disorder (Table V);

d. a new residual diagnostic category: "Catatonia not otherwise specified-NOS" is added, to facilitate the diagnosis in patients with psychiatric conditions other than schizophrenia and mood disorders or when the underlying general medical condition is not immediately recognized.

The ongoing debate

The changes carried out in the DSM 5 have been widely criticized [48]. According to some authors, the two categories of "Catatonia due to general medical condition" and "Catatonia NOS" easily overlap in clinical practice, while the excessive enlargement of the diagnosis of Catatonia NOS, even if useful to begin immediately a specific treatment, it would lead clinicians to neglect the search for a detailed diagnosis of the underlying condition. Moreover the duration criteria has not yet been considered. Despite the long standing debate, the proposal to create an independent diagnostic category for catatonia, completely detached from mood or psychotic disorders and somatic/neurological conditions, has not been accepted by the authors of the DSM 5. Different authors suggested that a non-coded specifier badly serves clinical practice and research. A specific diagnostic code would help the recognition of catatonia as a syndrome and would best fit for research on nosology, treatment and outcome [18].

Catatonia is still included in the "schizophrenia spectrum and other psychotic disorders" section. This position is somehow confounding when the syndrome is considered a specifier for other mental disorders or medical conditions.

TABLE V.
The possible diagnosis of catatonia in DSM- 5 (APA, 2013). *Possibile diagnosi di catatonia (APA 2013).*

1. Catatonia due to a general medical condition
2. Specifier "with catatonia" to:
a. Schizophrenia
b. Schizoaffective disorder
c. Schizophreniform disorder
d. Brief psychotic disorder
e. Substance-induced psychotic disorder
3. Specifier with another mental disorder (i.e. Neurovelopmental disorder, Bipolar disorder, Major depressive disorder, other mental disorders)
4. Catatonia disorder NOS (not otherwise specified)
Use the same set of criteria for the diagnosis of catatonia across the DSM- 5

Tandon et al. in a recent paper [55] have summarized the arguments in favor of the DSM 5 task force. The DSM 5 authors assumed that mental disorders (depression, schizophrenia, mania) associated with catatonia have a greater stability of course compared to catatonia itself. For example, patients with recurrent depression presenting an episode with catatonic features not necessarily manifest the same symptoms in the subsequent relapses. The same applies to schizophrenic patients, who may show catatonic symptoms during a period of illness and not in the subsequent course of illness. Therefore the choice of describing catatonia as a specifier of the primary psychiatric disorder seems to be more appropriate. Moreover classification of catatonia as an independent diagnosis could lead to an artificial increase of the percentage of comorbidity in mental illness.

Catatonia is characterized by a relatively uniform clinical picture in different clinical contexts, however differences in response to treatment seem to be related to the associated mental disorder and not to a specific set of symptoms belonging to the catatonic syndrome. For example BDZ and ECT are less effective when catatonia is associated with chronic schizophrenia compared to other diagnosis [56-58]. Moreover, the use of atypical antipsychotics, although generally not recommended in catatonia, can be justified when the syndrome is associated with psychotic disorders, thanks to their dopamine-stimulating property in the cortical prefrontal area [56 57].

In the final evaluation has therefore prevailed the opinion that the new version of the DSM 5 would adequately correct the deficiencies of DSM-IV and improve clinical diagnosis [59].

Conclusions

The DSM 5 approach to catatonia have disappointed a number of researchers and clinicians. This notwithstanding the DSM 5 task force, while not yet recognizing catatonia as an independent syndrome, has corrected those theories that affected negatively medical care and research for over a century. The new version of the DSM encourages clinicians to assess catatonic symptoms and signs in the most various mental disorders and to start immediately the most proper treatment even when the underlying cause is not immediately evident. This change is particularly useful in two clinical conditions:

- when an incomplete knowledge of the clinical picture or particularly complex diagnostic procedure do not consent to identify immediately the medical disorder associated with catatonia;
- when catatonic symptoms occur in the context of an autistic spectrum disorder and other developmental disorders [60-62].

In these cases the diagnosis of catatonia-NOS allows to

start immediately a correct treatment without unnecessary and harmful delays. Future studies will indicate if this approach to catatonia really help clinicians in the managing and treatment of this severe and sometimes fatal syndrome.

Conflict of interests
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Gender dysphoria in adolescents: the need for a shared assessment protocol and proposal of the AGIR protocol

La disforia di genere negli adolescenti: la necessità di un protocollo di assessment condiviso e la proposta del protocollo AGIR

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Summary

In the Center of Expertise on Gender Dysphoria at the VU University Medical Center in Amsterdam, a structured assessment and treatment protocol for adolescents with atypical gender identities is used. This multidimensional approach includes specific phases: psychological assessment, medical evaluation, possible psychotherapy, gonadotropin-releasing hormone (GnRH) analogues and cross-sex hormone therapy, which are differentiated according to age and specific requirements of each individual case. Recently, a collaborative study called AGIR (Adolescent Gender Identity Research) has been proposed by the Dutch clinic to allow international and cross-clinic comparisons with regards to referral background and psychological functioning, and to evaluate the treatment of gender dysphoric adolescents. An extensive assessment and timely treatment of adolescents with gender dysphoria seems essential to support the process of awareness and structuring of the dimensions of sexual identity, to prevent frequent associated psychopathologies and to improve quality of life by promoting more adequate psychosocial adaptation. Currently, transgender health care in Italy is characterized by isolated practitioners. Thus, it is particularly important to create specialised services that use a common protocol and that are coordinated at both the national and international levels in order to respond to the increasing number of requests in this age group.

Key words

Gender identity • Gender Dysphoria • Assessment • Intervention • Protocol • Adolescents

Introduction

There is perhaps no area of transgender health care that elicits as much controversy as the issues raised regarding the psychotherapeutic and medical needs of gender variant and gender dysphoric youth [1]. These issues are increasingly a matter of interest in the media and scientific literature. In particular, gender identity consists in the continuous and persistent sense of the Self as a male, a female [2], or as another gender, different from the binary of two genders. Gender Dysphoria (GD) is expressed by significant discomfort that is usually associated with the incongruence between gender at birth and gender identity [3], and represents a dimensional phenomenon that can occur with different degrees of intensity, of which the most extreme form is accompanied by a desire for gender reassignment (GR).

Aetiopathogenic theories are still uncertain, and debates on which treatment approaches to refer to are on-going, particularly when it comes to early GR in adolescents [4-5]. No unequivocal aetiological factor or set of factors determining atypical gender development has been found to date. With the current state of knowledge, it remains plausible that a complex interaction between a biological predisposition in combination with intra- and interpersonal factors contribute to a development of gender dysphoria, which may come in different forms and intensities [6].

Gender dysphoria can have an early onset, since preschool age, with extremely variable and hard to predict clinical outcomes. Children with atypical gender identity, in fact, represent a heterogeneous group, whose psychosexual and sexual identity development are still in progress [5]. The diagnostic criteria of GD in children and adolescents, as described in DSM 5, may therefore be indicators of a slight form of gender variance, or an early expression of a homosexual, bisexual, transgender, or gender queer development, which may or may not be accompanied by gender dysphoria [6].

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From current studies, it seems that only a percentage of 12-27% of children diagnosed with GD in childhood will also manifest gender dysphoria in adolescence and adulthood [8], and will ask for a complete GR [4-5]. To date, it is not known when or how gender dysphoria persists or desists. Clinical experience has shown that this often happens just before or just after the onset of puberty [6-8]. While childhood GD includes a wide range of outcomes, when it persists in the beginning of puberty, it will rarely desist into later adolescence and adulthood [6]. The WPATH (*World Professional Association for Transgender Care*) in its current 7th edition of the SOC [9] emphasises the differences between GD in childhood from that in adolescence and in adulthood, as it is characterised by greater fluidity and variability in outcomes, especially in prepubertal children.

At present, the majority of demographic information about transgender youth comes from research performed in the main clinics specialised in gender dysphoria: Canada, the United Kingdom, and the Netherlands [10-11]. There is virtually no record of the characteristics of children or teenagers who are gender variant, but do not have GD or who seek other help than in specialised clinics. Regarding the situation in Italy, a study was conducted by Dèttore, Ristori and Casale (2011) [12] on 350 children aged between 3 and 5 years with the specific aim of defining the main descriptive characteristics of gender identity in preschool age and to estimate the prevalence of atypical gender behaviour through the administration of the Gender Identity Interview for Children [13]. In this study, the prevalence of gender variant responses was found to be 5.23% in males and 3.93% in females, and 4.57% in the total sample [12].

Adolescents with GD, often have emotional and behavioural problems, self-harm, use and abuse of drugs, isolation from homophobic and transphobic families, higher suicide risk and are victims of violence with higher psychiatric comorbidities [14-16]. In particular, adolescents seen in gender identity clinics report higher rates of internalising psychopathologies compared with peers in the general population [15-17]. However, adolescents seen at the Dutch clinic report less psychiatric comorbidity than a clinically referred psychiatric population [15]. Adolescents who experience GD often suffer marginalisation and social stigma, issues that also affect gender dysphoric adults [18-19]. However, in the case of teenagers marginalisation and social stigma have a specific meaning (in terms of content and consequences) and must therefore be carefully addressed, taking into account the complex changing mechanisms on both the physical and psychological levels [20].

Early assessment of gender variant youth seems important to support awareness and structuring of sexual identity dimensions, to prevent associated psychopathology (if present), and consequently to improve the quality of life and psychosocial wellbeing [6].

Treatment of gender dysphoric adolescents is controversial and there is currently no consensus on psychological and medical intervention. This is likely related to the fact that there are no properly designed outcome studies evaluating psychological interventions, and only a few studies evaluating medical interventions. From the available studies, it appears that administration of gonadotropin releasing hormone (GnRH) analogues (at tanner stage 2-3) to suppress puberty and early cross-sex hormone treatment (between 16 and 18 years), followed by GR surgery at 18 years, can be effective and positive for both general and psychological functioning of selected adolescents with GD [6-21].

The Dutch Approach, including the AGIR protocol ("Adolescent Gender Identity Research" Group), proposed by the *Center of Expertise on Gender Dysphoria* of the *VU University Medical Center* in Amsterdam, is becoming a worldwide benchmark for evaluation and treatment of children and adolescents with GD [6].

Diagnosis

At present, the patho-biological basis of GD is unknown. Diagnosis is based primarily on psychological methods [20]. In May 2013, the DSM-5 was published with changes in name (*Gender Dysphoria*) and criteria, as follows:

A) A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months duration, as manifested by 2 or more of the following indicators:
   a) a marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or, in young adolescents, the anticipated secondary sex characteristics);
   b) a strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or, in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics);
   c) a strong desire for the primary and/or secondary sex characteristics of the other gender;
   d) a strong desire to be of the other gender (or some alternative gender different from one's assigned gender);
   e) a strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender);
   f) a strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender);

B) The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning, or with a significantly increased risk of suffering, such as distress or disability.

The diagnosis specifies two subtypes, with or without Disorders of Sexual Development (DSD). In the DSM-5 diagnosis, DSM-4-TR criterion C (the disturbance is not concurrent with a physical intersex condition) has been abandoned.

Differential diagnosis in adolescence

In adolescence, the main differential diagnoses in GD are ego-dystonic homosexual orientation, transvestic fetishism, disorders in the psychotic spectrum [5] and body dysmorphic disorder [22]. Not all adolescents with GD manifest a clear and explicit desire for medical/surgical GR, and they can be concerned about only some aspects of their gender identity or other dimensions of sexual identity in general. For example, adolescents with a homosexual orientation often have a history of cross-gender behaviours and interests in childhood. They may therefore have trouble distinguishing the dimension of sexual orientation from gender identity, or may find it difficult to accept their homosexuality due to more or less severe forms of internalised homonegativity [23]. In other cases, cross-dressing behaviours may be transient, occasional, compulsive, or associated with a state of sexual arousal (as in transvestic fetishism), and may be mistaken for a desire for hormonal/surgical GR. This can occur in individuals with or without psychiatric disorders. For example, in case of psychotic spectrum conditions, delusions of belonging to the other gender may be present. In cases of major psychopathologies, the opportunity for medical transition must be carefully evaluated and postponed in order to allow treatment of the psychiatric disorder and assess the levels of the psychosocial functioning over time [19].

There are also cases of individuals with GD who do not require a full transition, but rather try to integrate their own masculine and feminine aspects by adopting an androgynous or bi-gendered form of gender expression. In these cases, requests are more frequently oriented towards hormone therapy or surgery that only minimises the male or female phenotypic characteristics, but not forward a complete GR. However, these cases tend to appear more rarely in adolescence, probably because individuals with an early GD onset tend to have more extreme forms of GD. Considering the developmental processes of adolescence, which often include testing of different identities and expressions of the Self, special attention is required in the case of adolescents who arrive with a specific request for partial changes [20]. In these cases, forms of psychotherapy are probably more appropriate to clarify their situation and observe the evolution to ensure that any decision will be taken in a conscious manner. Even in cases of adolescents who have a clear diagnosis of GD, but who do not show any psychological skills of resilience and who do not have adequate social support, it is sometimes advisable to postpone cross-sex hormone treatment and/or surgery and try to create the basis for a positive outcome in the event of a possible GR [20]. Finally, the importance and clinical utility of a dimensional measure of gender identity/gender dysphoria in adolescents is clear. Even though GD has a low prevalence [7], the number of individuals who identify themselves as transgender individuals and who do not apply for GR seems to be far more prevalent than individuals who seek GR [24]. This makes a more sophisticated clinical approach of transgender applicants necessary instead of only assessing whether someone fulfils criteria for a complete GR.

Assessment

The assessment of GD is a complex process. However, the importance of an early and individualized assessment seems crucial in order to carefully evaluate the transgender identification, comorbidities and planning of an appropriate intervention [4-20].

The Dutch Protocol

In line with current guidelines (Hembree, 2009), health care professionals who work with GD in adolescents tend to refer increasingly to the Dutch Protocol, developed by the team at the Center of Expertise on Gender Dysphoria at the VU University Medical Center (VUMC) in Amsterdam. In particular, their model is described in the document *Caring for Transgender Adolescents in BC: Suggested Guidelines Clinical Management of Gender Dysphoria in Adolescents* [19] and in the more recent article *Clinical Management of Gender Dysphoria in Children and Adolescents: the Dutch Approach* [6-25]. The Dutch approach was revolutionary in this field as it was the first to offer early medical interventions to adolescents. Treatment was very closely monitored and based on on-going evaluation, as shown by the publications on the subject [6-25]. In particular, it is characterised by a multidimensional approach that includes different phases (*medical and psychological assessment*, *puberty suppression, and hormonal and surgical reassignment*). Ideally, it requires a multidisciplinary team consisting of child psychologists, child psychiatrists, psychometrists, paediatric endocrinologists, and – in the later surgical stages – plastic surgeons, gynaecologists and urologists. This approach emphasises that the assessment process has to be extensive, thorough and include different stages.

According to the Dutch Protocol, assessment of a gender variant adolescent requires psycho-diagnostic evaluation that includes general development, functioning in the different life areas and assessment of associated psychopathologies. Moreover, it is important to explore how the parents have raised the child, family history, family functioning and cultural and religious values. Specific assessment of GD should clarify whether the adolescent fulfils DSM diagnostic criteria for GD, excluding reactive forms or other differential diagnoses, excluding associated psychopathologies, and identify potentially predisposing and maintaining factors. It is also useful to reconstruct the onset of atypical gender behaviour, along with its characteristics and pervasiveness of expression in different life contexts. The methodology includes interviews with the adolescent and parents together with psychometric tests. During interviews with parents, one should assess the concordance of parental expectations and treatment objectives, as well as the opinions of both parents about their child's eventual psychosexual outcome, e.g. a future homo- or bi-sexual orientation. In the diagnostic phase, furthermore, the adolescent has to be accurately informed about the short and long-term consequences, and also regarding the limits of hormonal and surgical treatment to circumvent unrealistic expectations. The assessment also evaluates psychological and/or social risk factors that could possibly interfere (e.g. social phobia) with a good outcome of the intervention and that, if present, should be treated, sometimes even before the GD [1].

A particularly important aspect of investigation in the case of adolescents with GD is body image. It can happen that adolescents, who have received a treatment that has delayed pubertal development, are frustrated because they perceive the waiting period for the cross-sex hormone therapy as too long, as their bodies will not feminise or masculinise at the same pace as in their peers [20]. Moreover, greater internal conflicts and stronger negative emotions may be present if secondary sex characteristics are already developed before treatment. In fact, this frequently leads to breast binding or to other attempts of concealing breasts, penis and/or testicles. In these cases, emotions and feelings of shame, frustration and regret can be present because the treatment was not started earlier. Some adolescents may feel extremely confused to maintain their genitals of the natal sex, when the rest of their body is already changing, as a result of treatment with cross-sex hormones [20]. Regarding the therapeutic relationship, it is fundamental that the clinician holds a neutral attitude regarding any possible outcome in order to help the adolescent to explore openly his/her gender dysphoria and the desire for treatment [6].

According to the Dutch Protocol, there are three types of interventions in adolescents: fully reversible, partially reversible and irreversible [6-20]. Fully reversible interventions include therapeutic procedures whose effects are temporary, and allow to completely reinstall the initial situation in the case of suspension of the therapy. In particular, the administration of specific compounds, namely GnRH analogues, is considered. These are used in order to block puberty, or the processes of masculinisation/feminisation that characterises pubertal development. In the Netherlands, this possibility is given to carefully selected adolescents from 12 years on, who are at least in Tanner stage 2 or 3, live in a supportive environment, and have no serious psychosocial problems that interfere with diagnostic assessment or treatment [20]. Adolescents can thus explore their GD more extensively, and any desire to social or medical transition, without experiencing the distress of pubertal development. It is assumed that emotional problems that many young people with GD experience at the onset of puberty can thus be prevented [6-26]. Furthermore, blocking the development of secondary sex characteristics facilitates the transition to the desired gender role and later functioning in that role. For these reasons, this phase is considered as a part of the diagnostic process, and in the assessment phase it is explicitly discussed that such treatment can be interrupted at any time, thus leaving open all possible outcomes [6].

A recent study has shown that the overall psychological functioning of adolescents diagnosed with GD improved after an average time of two years from the beginning of treatment with GnRH analogues. In particular, a lower percentage of emotional and behavioural problems and depressive symptoms was found. However, this treatment had no effect on the levels of GD, thus supporting the hypothesis that adolescents who are accurately diagnosed maintain unaltered levels of GD in the remainder of adolescence and into adulthood, unless treated [19]. Previous studies have also shown that only cross-sex hormone therapy or GR surgery was likely to have an impact on the levels of GD [27]. These results were confirmed by a recent study in adolescents, which seems to show that GR surgery preceded by GnRH analogue treatment is effective in overcoming GD (de Vries, 2012). The concerns that early physical intervention will have unfavourable physical effects have not been confirmed [26-28].

Partially irreversible interventions refer to cross-sex hormone therapy, which represents the first step of an actual GR. According to the Dutch Protocol, adolescents are eligible for such treatment if they meet the aforementioned criteria and if they have at least reached the age 16 [6], unless there are medical reasons (e.g. expected tall height in male-to-females) to start somewhat earlier. Finally, completely irreversible interventions refer to sex reassignment surgery, the last step of the GR trajectory, which are possible after the person has reached the age of 18.

The AGIR (Adolescents Gender Identity Research Group)

Given the current difficulties in the assessment of gender identity in developmental age and considering the need for a shared protocol, the Dutch team has agreed with a number of centers to use a battery of tests that are clinically useful and enable cross-clinic research, e.g. permit evaluative comparisons or descriptions of populations [*]. As a part of the AGIR project, structured assessment of the adolescent's overall functioning and GD is performed. Specifically, the first part involves the administration of the following instruments:

- *Child Behavior Checklist* (CBCL) [29];
- *Youth Self Report* (YSR) [29];
- *Teacher's Report Form* (TRF) [29];
- *The Children Global Assessment Scale* (CGAS) [30].

The CBCL, YSR and TRF tests are part of the *System of evaluation on empirical basis* by Achenbach et al. (2008) and allow description of the child's behavioural and emotional repertory through the reports given by parents, teachers and the children themselves with the aim of evaluating the presence of potentially problematic behaviours listed within behavioural scales [29]. The answers can be rated on a 3 point scale (0 = not true; 1 = sometimes true; 2 = very true). The scales consist of about 100 items, grouped in 8 syndrome scales according to a dimensional approach: *Anxiety and depression* (evaluates the presence of depressive symptoms as sadness, irritability, loneliness, low self-esteem and feeling of not being loved); *Withdrawal and depression* (evaluates social closure, tendency to isolate, shyness and discretion); *Somatic complaints* (evaluates the tendency to express anxiety and concern through physical disorders as nausea, stomach pain and headache); *Social problems* (evaluates the difficulty within the relationships with peers as being teased and not getting along with peers); *Problems of thought* (evaluates the presence of thoughts and perceptions that are not reflected in reality); *Problems of attention* (evaluates the difficulty to maintain the concentration and the tendency to hyperactive behaviour such as impulsivity, irritability and motor restlessness); *Rule transgression behaviour* (evaluates the tendency to assume delinquent behaviours such as stealing, lying, setting fires and using alcohol or drugs); *Aggressive behaviour* (evaluates the presence of aggressive, provocative and destructive behaviours towards people or property). Moreover, it is possible to evaluate behaviour through the three general following scales: *Internalising*, *Externalising* and the *Total Problem Scale*. Finally, it is possible to identify 6 scales which are based on the categorical DSM-4-TR classification: *Affective problems* (dysthymia and major depression), *Anxiety problems* (generalised anxiety, separation anxiety and phobias), *Somatic problems* (somatisations and somatoform disorders), *Attention problems and hyperactivity*, *Oppositional-provoking problems* and *Behavioural problems*. The test score provides a profile of the child's competences, syndrome scales, general scales and *DSM oriented* scales. Regarding psychometric properties, Achenbach et al. (2008) can be consulted [29].

The CGAS [30] is one of the most widely used clinician rated scales for evaluation of the severity of disorders in young people. This is a one-dimensional measure of social and psychiatric functioning of children and adolescents aged between 4 and 16 years on a scale from 1 to 100. The CGAS is based on the adaptation of the *Global Assessment Scale* (GAS) for adults to children and adolescents, and can be used as an indicator of the need for activation of clinical services, as a marker of the impact of treatment, or as a single index of impairment within epidemiological studies.

The main objectives of the second part of the assessment are to specifically evaluate GD [7]. In particular, the following psychometric instruments are administrated:

- the *Gender Interview for Adolescents and Adults* [31]; this is a structured interview consisting of 27 items that explores gender identity and GD in the last 12 months in adolescents and adults. Specifically, gender identity and GD are conceptualised along a continuum, characterised by male and female poles, which includes various degrees of GD and gender uncertainty. For psychometric properties, the reader can consult Deogracias et al. (2007) [31];
- the *Utrecht Gender Dysphoria Scale* (UGDS) (Steensma et al. in press); this instrument consists of 12 items answered on a 5-point Likert scale, which specifically measures GD and the distress perceived by the individual in relation to daily confrontation with his/her gender. Higher scores indicate more severe GD. For the specific psychometric properties, Cohen-Kettenis and van Goozen (1997) [32] can be consulted (Steensma et al. in press);
- *Recalled Childhood Gender Identity Scale* [33]; this is a retrospective questionnaire which consists of 23 items designed to measure recalled gender-typed behaviours and relative closeness to parents during child-

[*] All the instruments used in the protocol of the AGIR research group in Amsterdam are currently being translated, adapted and validated by the authors of the present contribution, who form the reference research group for this protocol in Italy, and are part of the multicentre international research project managed by the Amsterdam group.

hood. For the specific psychometric properties, see Zucker et al. (2006) [33];

- *Body Image Scale* (BIS) [34]; this is a questionnaire that measures the satisfaction with one's body parts and is composed of 30 items divided into three subscales: primary, secondary and neutral. Higher scores correspond to higher levels of dissatisfaction with one's body. For the specific psychometric properties, see Lindgren and Pauly (1975) [34].

Conclusions

GD in adolescence is a complex phenomenon, whose origins are most likely multifactorial, that requires further study. Considering the growing demand for specialised services for GD in adolescence, it is important that mental health professionals who deal with these issues use assessment protocols that are comparable, both nationally and internationally, and increasingly based on empirical research. In this regard, the Dutch Approach, now largely included in the WPATH's SOC, and the AGIR project, provide an opportunity to perform comparative research between clinics [8].

Currently, mental health professionals are in a delicate and difficult situation when it comes to clinical decisions. They may intervene in the case of false positives, thus causing damage, or choose not to intervene, and as a consequence not alleviate the suffering of transgender adolescents who actually need these interventions. Lately, the age of the adolescents who come to the attention of specialists and require a GR has decreased considerably. It is not unusual, in fact, that adolescents 12 years old have an explicit request for a medical/surgical GR. Of course, this raises ethical and clinical issues with no easy solution [6-25].

In response to the criticism that has been formulated against the early treatment of adolescents starting with puberty suppression [5], the Dutch team underlines the importance of considering the consequences of non-treatment. Non-treatment does not represent a neutral option and, in some cases, can lead to negative consequences in the long-term for those people who have to wait until after puberty to begin hormone treatment. For example, individuals could be pushed to behave in an irresponsible and dangerous manner to have access to hormone therapy, confidence in professional help could be undermined and, finally, developmental processes and psychological functioning could be impaired. The philosophy *in dubio abstine* could therefore be harmful [20].

Structured guidelines for the assessment and treatment of gender dysphoric adolescents will assist professionals to help in resolving the adolescents' acute sense of unhappiness and developing the resources to live peacefully with their families and peers [4]. The Dutch Approach, taking into account all aspects of adolescent psychosocial functioning, not only aims to solve gender dysphoria, and eliminating it, but also to strengthen the resources of the person to ensure optimal psychological development and a good quality of life.

Conflict of interests
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Maintenance ECT for the treatment and resolution of agitation in Alzheimer's dementia

L'ECT di mantenimento nel trattamento e risoluzione dell'agitazione nella demenza di Alzheimer

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Summary

Background

Behavioural and psychological symptoms of dementia (BPSD) refer to the distressing, non-cognitive symptoms of dementia and include agitation or restlessness; wandering and non-specific behaviour disturbance e.g. hoarding; verbal or physical aggression; anxiety; depression; psychosis, delusions, hallucinations; repetitive vocalisation, cursing, screaming and swearing; sleep disturbance; shadowing; sundowning.

Clinical case

We report the case of a patient with advanced stage Alzheimer's dementia with severe BPSD not respondent to several trials of antipsychotis, anxiolytics and mood stabilizers. The patient was treated with acute and maintenance bilateral ECT.

Conclusions

This case represents a successful use of acute and maintenance ECT in the treatment of BPSD, in particular psychomotor agitation, associated with Alzheimer's dementia. According to our experience, it is important to manage this psychiatric manifestations with ECT, especially in those cases in which the psychopharmacological treatment alone does not give satisfactory results in clinical improvement.

Key words

Electroconvulsive therapy • Dementia • Agitation

Behavioural and psychological symptoms of dementia (BPSD) refer to the distressing, non-cognitive symptoms of dementia. BPSD include symptoms of disturbed perceptions, thought content, and changes of mood or behaviour compared to baseline [1]. The spectrum of BPSD includes agitation or restlessness; wandering and non-specific behaviour disturbance, e.g. hoarding; verbal or physical aggression; anxiety; depression; psychosis, delusions, hallucinations; repetitive vocalisations such as cursing, screaming and swearing; sleep disturbance; shadowing; sundowning [1].

BPSD are observed in up to 90% of patients with dementia: agitation and aggression are present in 60-80% of subjects with Alzheimer disease [2].

Primary intervention, after failure of non-pharmacological measures, is the use of antidepressants, mood stabilisers and antipsychotics [3 4]. Unfortunately, there are few controlled trials in patients with dementia, and atypical antipsychotics have been shown to increase overall mortality; moreover, patients often are unable to tolerate the side effects of these medications [5].

Electroconvulsive therapy (ECT) has been shown to be effective in the treatment of BPSD [6].

Herein, we report a case of successful use of ECT as acute and maintenance treatment for BPSD in a patient suffering from advanced stage Alzheimer's dementia. Mrs E.S. is a 76-year-old white female, with negative psychiatric history, but a clear hyperthymic temperament and a 3-year history of severe Alzheimer's dementia. Psychiatric family history was positive: the older daughter had hyperthymic temperament and the younger suffered from severe social phobia and later developed an episode of psychotic mania, treated successfully with lithium and olanzapine. Mrs E.S. was admitted to the psychiatry unit for confusion, severe psychomotor agitation and restlessness, insomnia, mood lability with weeping and anger, repetitive vocalisation, cursing and swearing. Because of her behaviour, the management of the patient by relatives and a visiting nurse at home failed (Activities of Daily Living, ADL = 0). Therapeutic trials of trazodone, promazine, zuclopenthixol and valproic acid were ineffective. On admission, medications included quetiapine 800 mg/day, lithium 900 mg/

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day, valproate 1,000 mg/day, clozapine 200 mg/day and niaprazine 30 mg/day.
Cognitive screening with the Mini Mental State Examination (MMSE) was not possible because of agitation. Laboratory exams were normal. A head computerized tomography (without contrast) showed diffuse cortico-subcortical atrophy with secondary ventricular enlargement. The patient was treated with a course of 3 applications of ECT with bitemporal lead placement, with resolution of confusion, psychomotor agitation and behavioural disturbance. At home, the patient continued therapy with quetiapine and prometazine. In the next 7 months, the patient was admitted to the hospital three times because of behavioural disturbances, and was treated with a total of 8 applications of ECT (6 bitemporal, 2 bifrontal). Since the effect of ECT was rapid and effective, but short-acting, with the patient relapsing approximately every 2 months, we started maintenance ECT (2 applications every 45 days) for the next 6 months. During maintenance ECT, the patient showed relapses and remained in good behavioural control. Quetiapine was tapered to 50 mg/day and continued for the following 2 years. No further ECT was indicated. The patient died at the age of 80 years for progressive kidney failure.
Discerning the aetiology of behavioural and mood changes in the setting of advanced dementia is difficult: agitation and aggression may be the result of impairment of cognitive functioning, psychosis, anxiety, mania, agitated depression, physical illness or discomfort, or a side effect of medical therapy. Although depressive disorders remain the most common indication for ECT in the elderly, a growing body of literatures has identified ECT as an effective intervention for severe refractory agitation in patients with dementia [7]. We believe that randomised, controlled trials with ECT are necessary to further assess its efficacy for this indication.

Conflict of interests
None of the authors have anything to declare.

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Aggression as a psychopathologic dimension: two case reports

L'aggressività come dimensione psicopatologica: due casi clinici

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Summary

Herein, two case studies are presented in patients who were admitted to hospital for violent behaviour with the objective was determining whether risk factors of hetero-aggressive behavior in psychiatric patients, as outlined in the international literature, were present in these two cases. After initial presentation of the clinical situation of these two patients, risk factors were identified. Thereafter, we attempted to outline the motivations and context that had driven the violent behavior. We conclude that accurate knowledge of the history and life of the patient and the evolution of the condition over time is indispensable for cure, both in order to develop a treatment intervention strategy that is integrated and focused on the patient's needs, and to prevent future incidents of aggression.

Key words

Aggression • Violent behaviour • Psychiatric patient

Douglas and Skeem [1] stated the difference between "risk status" and "risk state", indicating the former as the inter-individual level of risk largely based on "static" risk factors – i.e., gender, history of violence, childhood abuse and psychopathy – and the latter as the intra-individual level of risk widely determined by "dynamic" risk factors such as stress, emotional responsiveness, hostile rumination, impulsiveness, substance abuse and lack of insight. According to the authors, focus must be on dynamic risk factors because of their capacity for transformation and development. It is essential to keep in mind that risk factors do not act as a single cause in an event; they always interact with each other [2] and their interactions can be direct, indirect or mediated by a third variable. Aggressive behaviour, in fact, is multifactorial: it is a transactional process that reflects a multiplicity of causal risk factors. Nowadays, when evaluating risk factors of violent behaviour, four dimensions are considered: individual and demographical, clinical, biological and contextual [2 3]. With regard to demographic factors, some authors [4] assert that the association between violent behaviour and psychiatric diagnosis cannot be represented by these variables. As James et al. [5] observed, age is a purposeful variable in predicting the risk of violence: young patients (≤ 25 years) are at higher risk than others. Similar results have been reported in numerous others studies [6-11]. Pearson [11] and Tardiff [12] observed that the peak in violent crimes was reached in 20-year-old individuals. In a study by Waldheter [13], the correlations suggest that individuals with a lower level of education are more likely to be implicated in violent episodes inside the psychiatric unit, and that men commit more violent acts than women. Bjorkly [14] affirms that psychotic men are more violent than women with the same disorder. Allen identifies belonging to the male gender as a violent behavior risk factor in psychiatric population. This study agrees with the MacArthur's Risk Assessment Study [16] in that a history of violence and abuse increases the risk of violent behaviour and confirms the empirical connection between a past of violence with a future of violence.

Caprara, Barbanelli and Zimbardo [15] investigated the multidimensionality of aggression, focusing on the different processes and mechanisms that form its different expressions; they consider that comprehension of the interactions between interpersonal and personality aspects will prevention and identification of points for intervention. They classified a triad of factors that appear frequently in data collected in different countries: irritability, hostile rumination and tolerance for violence. Two other factors emerged from second order factor analysis, namely "emotive responsiveness" (a temperamental factor) and "positive valuation of violence" (a specious type of aggression). The presence of emotional responsiveness and hostility creates what the authors define as the "dangerous zone of violence", a concept also sustained by other authors [1 10 18]. Another important aspect regarding aggression is impulsivity: Barratt et al. [17] iden-

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tified two different types of aggression: "impulsive" and "proactive". The first one is described as a "reaction of hair-trigger" to a provocation that leads to an abnormous aggressive reaction, while the second is described as an act accompanied by a poor quality emotive response. Subjects belonging to the first group have a better therapeutic response when treated with mood stabilisers. Those with a high level of impulsivity exhibit multiple neurocognitive deficits characterised by reduced flexibility, poor planning capacities and poor verbal learning. Some researches focused on the influence that some social factors may have on aggressive behavior. Ferguson et al. [18] observed that social isolation, associated with depression, is a potential risk factor. Silver [19] suggested that the use of theories from the forensic field may allow for a more complete approach to the study of violence in people with mental disorders. For example, the theory of social learning [20] focuses on the effects that behaviour, learning habits and beliefs have on aggressive behaviour. This supports the importance of Lazarus' stress theory [21], according to which highly stressed individuals are more likely to experiment negative feelings such as anger, fear or frustration. A constant involvement in conflictive relationships may represent a type of chronic stress: people with serious mental disorders – especially those who experience delirium or hallucination, or those who use drugs – probably introduce negative elements in their relationships. In their study, Swartz et al. [22] observed that non-compliance with medical treatment and concomitant substance abuse in patients with major mental disorder is associated with serious violent acts. In several studies, substance abuse is also considered to be a strong predictive factor for the non-psychiatric population, but comorbidity with mental disorder, substance and alcohol abuse increments the risk of violence [1 10 11 14 16 25 26]. Lack of awareness of the disease and need for medical care have been associated with non-compliance to treatment and relapse. These results are also reinforced by Elbogen et al. [27]. In their study, it was observed that the perceived necessity for treatment was associated with a reduction in the level of violence in patients with a mental disorder. Nevertheless, more recent research has not found a direct correlation between a lack of insight and violence. MacArthur's Risk Assessment Study underlines the effects that substance abuse and mental disorder have on aggressive behaviour:

- substance abuse is correlated with a diagnosis of major mental disorder only in 40-50% of cases;
- substance abuse increases the frequency of both serious violence and other aggressive acts;
- there are no differences in violent behaviour between the clinical group with substance abuse and the control group without substance abuse;
- the clinical group has symptoms of substance abuse more often than the control group.

Until today, research on violence has not produced an unequivocal image of variables connected to mental health that are associated with the risk of violent behaviour. Regarding specific clinical factors, it has been thought that depression is associated with aggression, especially within parent-children relationships. Mammen et al. have observed that aggressive behaviours in this clinical group seemed to be impulsive and guided by a reaction to negative situations. Furthermore, Berkowitz suggests that depression may contribute to aggression from the moment that it carries negative emotions and thoughts. It is then probable that in some people depression may increment sensations of anger, principally towards the source that generated them. Ferguson's study, on another hand, asserts that this pathology is not significantly associated with aggression, at least inside psychiatric units.

Several studies have examined the correlation between disorders such as schizophrenia and bipolar disorder and violent behaviour. Persistent aggressive behaviour interferes with treatment and increases the burden of disease for both the caregivers and society. A problematic point is the complexity of violence. In fact, studies on violent behaviour in patients with schizophrenia have not discriminated between different types of violence. It has not been considered that violent acts may originate from different motivations, nor that for this reason different types of treatment may be considered. Results show that the incidence of violence is higher in psychotic patients, but only in comorbidity with alcohol or substance abuse [11 15]. Patients with mental disorders who also use substances or alcohol are more likely to be involved in violent behaviours than those who do not suffer from a mental disorder, but who abuse substances or alcohol [28]. Mac Arthur's Risk Assessment Study underlines how a diagnosis of major mental disorder is associated with a lower level of violence than a diagnosis of personality disorder or a diagnosis of adjustment disorder. In that study, the presence of delirium, regardless of its contents, is not associated with violence: neither hallucinations in general, nor those imperative in itself, have been shown to increase the risk of violence. Nevertheless, if the 'voices' specifically order a violent act the probability of an aggression will increment. Nolan et al. [29] found that, even if 20% of the sample group reported the presence of florid specific symptoms (for example, auditory hallucinations) in the moment of aggression, even when these florid symptoms were not present, the disorganisation and confusion may have brought them to misunderstand their victim's actions and, for this reason, to respond with aggression. Moreover, an Italian study supports the idea that aggressive behaviour correlates positively with paranoid schizophrenia and maniacal disorder [30]. Binder and McNeil observed an increase in risk for hostile and suspicious patients and for those who have thought disorders. Steadman consid-

ers the nature of delirium and hallucinations as potential areas when assessing risk factors.
Link et al. [4] identified a concept they termed "threat control override" (TCO) to explain the possible effects of some psychotic symptoms that lead to violence. They sustained that when a person feels threatened and when his inner control is compromised, violence will be the primary response. Their study shows that the presence of "TCO" symptoms is significantly associated with aggressive acts not only in the psychiatric population. The study by Swanson, Borum et al. [31] supports Link's results. They also observed that people who feel threatened and, at the same time, incapable of controlling their impulses, are involved twice as often in violent behaviour. Beck observes that the presence of delusions correlated to violence is rare, but, when it happens, seems to steer violence; therefore, in more than half of the cases, delusions are of the "TCO" type. In their study, Teasdale et al. [32] observed that this group of symptoms increases violence in male patients, but not in female patients.
According to Jungiger [33], hallucinations that instigate delusions are the most obvious source of violent behaviour in patients with schizophrenia. Zisook et al. [34], on the other hand, observed that patients with imperative hallucinations are not more violent than those without these types of hallucinations [31]. In a recent review [35], the association between schizophrenia and violence was summarised in the following points:

- the risk of violence increases in individuals with schizophrenia and other psychoses;
- comorbidity with alcohol or substance abuse increases risk;
- there are no significant differences in risk estimates with respect to some variables such as the type of disorder (schizophrenia versus psychosis) or the place where the study was carried out;

the increased risk of violence in patients with schizophrenia and comorbid substance abuse is the same as that in individuals not suffering from schizophrenia, but with substance abuse problems. Another study [36] observed that the relation between schizophrenia and violence is minimal unless it is not related to substance abuse. These suthors also investigated the risk of violence in schizophrenic patients, underlining the importance of factors such as criminal history, sociodemographic and clinical characteristics and substance abuse. Neuro-cognitive factors, not often included in research investigations, are also of the utmost importance. Serper and Reinhart identified three groups of biological-cognitive factors associated with violent acts in schizophrenic patients: neurocognitive skills, neurocognitive consciousness and attitudinal cognition (e.g. hostile attribution biases, attribution of benevolence or malevolence to voices, the impression of being controlled by others). A person with an executive dysfunction may not possess the abilities of behavioural inhibition necessary to cope with the presence of symptoms and other stressful events that accompany acute psychosis and hospitalisation: this can lead to an increase in aggressive manifestations. However, some authors do not agree with these conclusions [42]. In Italy, Raja et al. [37] assessed the relationship between hostility and violence in psychiatric patients in psychiatric units, reporting that violent behaviour is lower than in other countries. Risk factors associated with hostile and violent behavior include: young age at onset of the disorder, being single, not having children, a lower score in global operation (GAF) and a high BPRS (brief psychiatric valuation scale) score. In addition, patients have a wide range of psychotic symptoms (suspiciousness, hostility, hallucinations, thought disorder) and a lower capability of insight in the control of aggressive impulses than non-violent patients. However, these results refer to the risk of violence in psychiatric patients in psychiatric units. Berti and Maberino [38] carried out research with the purpose to highlight the risks and hypothesise improvements in the treatment and prevention of hetero-aggressive acts. Psychiatrists, nurses and psychologists were administered a questionnaire that investigated whether they had suffered attacks or personal injuries. The results showed that the principal risk factors that need to be taken into account to prevent violence are those both related to the acute and chronic aspects of the patient's disease, both factors related to the therapist.

Case reports

Two case reports are presented and then interpreted using data available in literature.

Case #1

Name: Angelo.
Age: 42.
Pathology: Paranoid schizophrenia (DSM IV-TR) Angelo is 42 years old and has been living in a Therapeutic Community for a few years. He is an only child and his parents divorced when he was 1 year old. They apparently divorced because his father was epileptic and could neither work nor take care of his family, so the wife achieved a dissolution of marriage. In spite of this, Angelo continued to have a regular relationship with his father until he was 18. At this time, he started having psychotic symptoms.
Angelo lived with his grandparents until he was 6 years old. When he started primary school, he moved back with his mother. His mother says he was lazy, that he had many learning difficulties and didn't socialize easily. She says he was dramatically lonely, to the point of seeming retarded. In fact, Angel had to repeat the fifth year; how-

ever, his scholastic situation improved and he managed to attend a professional high school. Nevertheless, he never established any strong relationships and continued to be extremely lonely.
When he turned 18 an intensification of these peculiar features of his character defined a psychopathologic beginning that resulted in an acute outbreak at the age of 22. At this time, he had just returned from a long journey in India that he had undertaken to improve his knowledge of martial arts and oriental philosophy. He was hospitalised because of poorly constructed delusional ideas and deep behavioural disorganisation (e.g., he believed to be in a strong relationship with the Indian embassy and to have rescued the Pope, Gandhi and Kabir Bebi). He was discharged 8 months later.
The Local Mental Health Centre was responsible for his care, but he was a difficult patient. He was not able to understand the pathologic nature of his thoughts and he often avoided taking his medicines and going to doctors. He spent a lot of time at home with his mother, living in a sort of symbiosis with her; apparently, they didn't even open the door to healthcare operators.
During the next years, he was frequently hospitalised for his delusional disease, the last time in 2004. At that time, he had manifested aggressive behaviour towards his mother. After this episode, the attending psychiatrist, considering the complexity of the situation, disposed his recovery in a Family Home.
At first Angelo seemed to adapt well to life within the Family Home, attending his normal activities and becoming a reference point for other guests thanks to his skills in computers and technology. He was still reserved and uncommunicative, but he continued to dedicate himself to his main interest, Ninja philosophy, studying it on the internet.
During these years, everything went fairly well even if he was often admonished to respect the rules of living together. He took his medicines and regularly went for visits home. He was then again admitted to Psychiatry because of an aggression towards an operator motivated by an insignificant reason: he had only been asked him turn down the television volume.
He was admitted as "Involuntary Psychiatric Treatment". A strong delusional idea related to his identity came up. He thought he was a black Ninja, a strong hero with special powers. Having taken that into account, we asked him to examine in depth the meaning of what he is saying and also to tell us what happened in the Family House. Angelo's behaviours and relational modes are those of a black ninja: his sentences are frequent but very short, combined with typical ninja mimicry. Our meetings often take place in his room, in the infirmary or in the hall. He focuses mainly on particular themes, such as explanations on his medical therapy, changes in his blood pressure or heart rate, or on why he cannot get out of the division or go to his mother's. The tone used with the patient reveals an understanding of his situation, contained by the physical and relational bounds of the division: the operators create a constant emotional containment environment around the patient, never leaving him by himself. The feedback of the security of the division and his experimentation of the "security" of his borders, combined with an increment of neuroleptic therapy, helped the patient to progressively take distance from his delusional disease, eventually leading to him talking about this character in the third person and referring to himself as a victim of a strong possession, impossible to outflank. He is presently in a Therapeutic Community, and delusional ideas are no more prosperous or strongly invasive. Finally, the patient seems to be cooperating in implementing a new treatment plan.

Case #2

Roberto is the fifth of seven children. Both his parents are still alive. He attended secondary school and did not continue his studies. Psychiatric anamnesis is positive: according to what the patient refers, his father was depressed and violent. One of Roberto's sisters suffers from depression. We do not have access to much information on Roberto's family and he speaks very little about them. His psychiatrist does not consider psychotherapy a useful approach because of his lack of capacity for insight. Roberto is married and has two children: a teenage girl and a boy who just turned 18; both are being followed by a speech therapist from the children's neuropsychiatry local service. His wife has undertaken psychotherapeutic treatment. Roberto worked in a factory and in 2004 he was managed by the Local Mental Health Center. At the time, he told the psychiatrist he felt tired and stressed because of his work: he was waiting to receive a disability leave because of partial deafness. He also said that he often quarrelled with his employer. Later on, he was offered a pre-retirement settlement that he accepted. From that moment on he has worked in a market at an acquaintance's fruit stand. Roberto's family is thus supported by his wife's salary (she works as a cleaner in a cleaning company), by his invalidity pension and by the subsidies the family receives for the children. Roberto referred symptoms of nervousness, mood deflection, tiredness, irritability and reactivity to his psychiatrist. He said he felt as if someone was calling him and to "turn and see a shadow", or "see some spider on the wall". He refers periodic and frequent quarrels with his wife, all of which without any striking expressions of violence, until the day Roberto threatens his family with a hammer. His wife, frightened, called the police. This episode was apparently triggered by the relationship with his children, and in particular by the fact

that he felt he was starting to lose control over them. After the incident, he was hospitalised in a Psychiatric Unit where it emerged that the tension inside the family had been building up for a considerable time, caused by their economic situation: Roberto felt incompetent and a failure. Roberto's sister has always played the role of a mediator between the couple. After the incident, Roberto's wife moved in with Roberto's sister. After being discharged, the patient went for some time to the local day hospital. The treatment has helped Roberto to improve and to control impulsivity. The team that follows him, along with his psychiatrist, after thoughtful considerations, have reached the conclusion that the patient reacts with violent and impulsive modalities in stressful situations. The event that led to the hospitalisation seems to be more related to the fact that his son had reached legal age and that Roberto felt his paternal authority was threatened leading to persecutory delusional symptoms. The assumption is that Roberto's story is the story of a victim of abuse who becomes an abuser: social relational modality learnt in the past and reintroduced in the present.

Conclusion

In both the present cases, the risk factors that have emerged are: male gender, low socio-economic status and earlier violent episodes (even if Roberto, in contrast to Angelo, has only threatened violent behaviour). Regarding dynamic risk factors, we find the presence of a stressful context: this element supports Silver's theory [19] according to which highly stressed individuals experience major negative effects such as anger, fear and frustration, and that these may induce them to exhibit violent behaviour. Impulsiveness was also a risk factor in both cases: referring to Barratt's article [17] it would be an impulsive type of aggression, defined by the authors as a "reaction of hair-trigger" to a provocation. They put into light how this type of patient is characterised by impulsive aggressiveness and seem to show multiple neurocognitive deficits: poor cognitive flexibility, poor planning skills and poor verbal learning. Regarding the presence of suspiciousness and hostility, both patients have a clinical diagnosis that falls in the paranoid spectrum, even if with different severity. Angelo, in fact, has a diagnosis of paranoid schizophrenia, while Roberto has a diagnosis of paranoid personality disorder. The relationship between these two diagnoses and violent behaviour has been studied by many authors, and Searles will be discussed first. This author in "Scritti sulla Schizofrenia" [39] examining the causes of anxiety in paranoid Sshizophrenia. Searles explains how in psychotic patients, threatening feelings present themselves modified by a series of ego defences, that although intended to protect the patient, at the same time distort his experience in a strange and frightening manner. The patient, in fact, does not experience anguish as such, but confusedly feels that several elements of the environment possess a sinister meaning, a malicious charge against him. For the patient, the persecutory figure represents the person that is part of his living environment, and that more easily lends itself to personify those attributes that the patient feels he must repudiate in himself and project into the outside world. Therefore, the patient cannot give up taking care of that person because:

- it would mean losing important components of his personality;
- that person is necessary for him as a receptacle for these negative emotions;
- he cannot reconcile with that person because that would mean to accept in his self-image certain qualities that he repudiates.

The patient then lives under a constant threat of not only external persecutors, but also of "introjects" that he carries within himself, mostly without knowing it. These "introjects" are distorted representations of people who belong to the outside world, perceived as invasions of one's self. It can be argued that the patient lacks an authentic experience in the form of fantasy: in fact, whenever he experiences a new combination of thoughts or mental images, he immediately believes that it is a representation of external reality. He is suspicious because suspicion is the only means to develop and evaluate the data that come from a world staggering in its complexity. By studying the relationship between paranoid schizophrenia and aggression and referring to the theory of mind (ToM), Giovanbattista et al. [40] suggested that these patients have difficulty in accurately monitoring the intentions of other people. Their undermining in the use of contextual information would lead them to make incorrect inferences about the intentions of others. Studies have shown that patients with paranoid schizophrenia are more prone to violence than other groups of schizophrenics [41 45]. In agreement with the studies of Dietz & Rada [42], Kennedy [44] found that sudden aggressions are carried out by apparently compensated patients suffering from paranoid delusions. In fact, Angelo, in a moment of apparent psychic compensation, had suddenly attacked a nocturnal operator in the throes of a persecutory delusion. In the forensic field, Esbec et al. analysed the relationship between paranoid personality disorders and aggression, and observed that these subjects are permanently suspicious and hypersensitive to shame, with a tendency to attribute malevolent intentions to others. A paranoid personality commits an aggression often due to misinterpretations and overreactions to daily situations, especially when the possible victims put in place physical or verbal actions that are interpreted as a personal aggression. In this regard, we think

that the fact that Roberto's son turned legal age and manifested actions of independence, and defended his mother against his father, may have led the patient to experience an intense feeling of shame accompanied by strong anger due to the fact that his teenage daughter came home wearing makeup. It is assumed that the feeling of losing control over his children, experienced as a personal attack, may have led Roberto to act aggressively towards his wife and family. In agreement with the idea of the importance of thorough knowledge of the patient's personal and family history, beyond the presence of individual risk factors, it is useful, in retrospect, to trace the presence of factors and circumstances that induced the aggressive actions in these two patients. In Angelo's situation, the conjunction of his mother's illness (who was progressively going towards dementia) and the renovation of the house where he had always lived may have favoured psychic disintegration accompanied by a deep sense of anguish for which the delirium becomes a channel for its containment. As for Roberto, the climate of violence (especially from his father) in which he grew up could have led to learning attitudes and violent behaviours as the only answer to feelings of anger and frustration that characterised the exact period in which the patient acted aggressive behaviour. It is assumed that what made the patient lose control, rather than delusional persecutory symptoms, was the coming of age of the child and the consequent perception of his paternal authority becoming less. The assumption then is that the story of Roberto is a story of an "abused" person who becomes "abusive": a historical-social-relational mode learnt in the past and re-launched in the present. We conclude that accurate knowledge of the history and life of the patient and evolution of the condition over time is an indispensable key to cure, both to develop treatment strategy that is integrated as much as possible and focused on the patient's real needs and prevent future incidents of aggression.

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Integrated treatment of schizophrenia

Il trattamento integrato della schizofrenia

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Summary

Psychosocial therapies play an important role in the treatment of schizophrenia. These therapies are aimed at improving the functioning of the patient in the community, which in turn can lead to clinical improvement, such as reduction in the number of relapses or hospitalizations. Substantial evidence supports the use of many psychosocial therapies in schizophrenia, including cognitive behavioral therapy, assertive community treatment, cognitive remediation and functional skills training.

The customization of pharmacological therapy in schizophrenia, besides the experience of the clinician and individual preferences of the patient, should be based on three sets of objective data: 1) clinical predictors of response to therapy; 2) predictable side effects of therapy; 3) pharmacogenetic and pharmacogenomic data.

It has been made a considerable effort to improve adherence to antipsychotic treatment through the development of drugs with better tolerability, in formulations that enable long-term administration of the drug, including injectable long-acting (depot) antipsychotics. In recent years the development of these formulations of atypical antipsychotics and the promising results obtained in clinical trials are changing the attitude toward these drugs, traditionally reserved for patients with repeated non-adherence to treatment.

Key words

Pharmacological treatment • Rehabilitative and psychosocial psychotherapy

Pharmacological treatment, rehabilitative and psychosocial psychotherapy

S. Galderisi

Introduction

Schizophrenia is caused by complex interactions between biological, genetic and environmental factors; as a consequence, patients affected by the disorder should receive integrated treatments that include drugs and psychosocial therapy, care of physical health and treatment of comorbidities. In general, drugs are administered in the initial phases of schizophrenia when symptoms lead to an individual to consult psychiatric services. Psychosocial therapies are frequently not initiated until the appearance of uncontrolled symptoms. This model could change, however, once early diagnosis and timely therapeutic intervention become more common and non-pharmacological treatments can be initiated at an earlier stage. An integrated and multifaceted approach involving drugs, psychosocial interventions and attention to environmental circumstances can improve the outcomes of schizophrenia[1]. Thus, the psychiatrist should be part of a multidisciplinary team, composed of mental health professionals and other medical specialists, as well as providers of social services and other relevant entities (e.g. authorities who organise housing and employment).

Treatment with antipsychotics

Antipsychotics are a fundamental element of treatment of schizophrenia [2]. Undoubtedly, they are very effective in reducing the positive symptoms of schizophrenia. However, at present, the available antipsychotics have significant limitations (Table I); in particular, negative symptoms and cognitive alterations are not treated adequately, and many patients continue to present persistent psychotic symptoms. In addition, the lack of insight that accompanies schizophrenia is a partially unsolved problem. Clinical studies have consistently demonstrated that antipsychotics reduce positive symptoms such as delirium and hallucinations [3 4]. In this regard, large studies have demonstrated that second-generation agents are at least as efficacious (if not more so according to some studies) than first-generation antipsychotics, and that they are generally

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better tolerated with a reduced propensity to induce adverse effects such as motor symptoms; accordingly, they are associated with better compliance [3 5]. The safety profiles of older and newer agents, however, are significantly different [5].

Antipsychotics have been shown to be effective in the treatment of acute psychotic episodes [6]. About 85% of previously untreated patients show improvement of symptoms and 60% remain in remission at 3 years[7]. Effective, timely treatment of psychoses in the initial phases can avoid a long duration of untreated psychosis, which is associated with poorer clinical and social outcomes [8 9]. Maintenance therapy reduces the risk of relapse in patients with schizophrenia. An analysis of 65 clinical studies involving more than 6000 patients with schizophrenia demonstrated that maintenance treatment reduces the incidence of relapse and hospitalisation by around 60% (Fig. 1) [10]. It is important to highlight that this analysis also showed that the number needed to treat (NNT) of pharmacological therapy is related to adequate psychosocial therapy: under these conditions, in fact, treatment of only 3 patients for 7-12 months can prevent another relapse and treatment of 5 patients can prevent another hospitalisation [10].

In some patients, relapse can delay or halt progression of disease [11]. Moreover, by preventing relapse and improving insight, antipsychotics can assure a period of stability and facilitate the introduction of additional treatments such as psychosocial therapy [12]. There is evidence that the greater the improvement of symptoms after the start of pharmacotherapy, the greater the probability of a good response to psychosocial therapy [12].

Behavioural symptoms such as hostility and aggression are common in schizophrenia, and there is evidence that these symptoms are susceptible to antipsychotic drugs [13]. In general, good adherence to therapy seems to be associated with low levels of aggression, and persons with schizophrenia who adhere to therapy and are clinically stable do not seem to be more violent than the general population [13]. Suicidal behaviour is present in about 50% of affected individuals and about 5-10% of persons with schizophrenia commit suicide. Clinical studies with some antipsychotics have shown that they are associated with a reduction in suicidal behaviour [14].

Limitations of antipsychotics

The negative symptoms of schizophrenia, such as apathy, anhedonia and decreased emotional expression, can be present at the onset of disease and may represent the predominating symptoms; in fact, in around 70% of cases these symptoms develop before positive symptoms [3]. In reality, there is evidence to support the existence of a form of disease (deficit schizophrenia) that identifies a subgroup of patients characterised by the presence of primary and persistent negative symptoms [15]. The available antipsychotics have a limited effect on negative symptoms and are ineffective on primary and persistent symptoms [3]. This limitation is an important problem since negative symptoms are associated with compromised employment and social functioning, and are thus a significant obstacle in maintaining an independent life [16].

Almost all patients with schizophrenia have deficits in cognitive function, which affects domains such as verbal fluency, memory, attention, velocity of elaboration, ability to assign priorities and make decisions [3]. Such deficits present early in the course of disease, in general years before the appearance of overt psychosis, and are strong predictors of compromised social functioning and unfavourable outcomes. Unfortunately, currently-available antipsychotics have limited impact on the cognitive symptoms of schizophrenia: any improvements observed appear to be correlated with a reduction in other symptoms rather than to direct effects on cognitive ability [17 18].

Antipsychotics are associated with several collateral effects that can be severe and limit adherence to therapy, thus decreasing the possibility of recovery (Table II) [3]. Individual antipsychotics differ in their safety profile, but some adverse effects, such as motor symptoms and metabolic hormonal disorders, are common to all these

TABLE I.
Potential benefits and limitations of current antipsychotic medication (from Fleischhacker et al., 2014, modified) [1]. *Possibili benefici e limiti degli attuali farmaci antipsicotici (da Fleischhacker et al., 2014, mod.) [1].*

Benefits	Limitations
Reduction of positive symptoms	Limited efficacy against negative symptoms
Treatment of acute episodes	Inadequate treatment of cognitive impairment
Reduced risk of relapse	Troubling side effects or tolerability issues
Provision of stability and a platform for other treatments	Low acceptability to some patients • Poor adherence • Negative perceptions
Reduction of aggression and hostility	
Reduced suicidal behaviour	

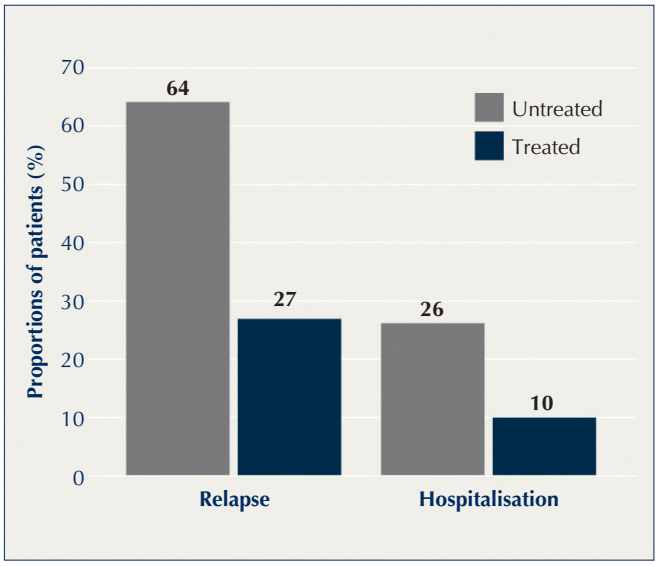


FIGURE 1.
Long-term treatment of schizophrenia (maintenance) significantly reduces the number of relapses (7-12 months) and the number of hospitalizations in patients with schizophrenia, compared with placebo (data from a combined analysis of 65 clinical trials) (from Leucht et al., 2012, modified) [10]. *La terapia antipsicotica a lungo termine (di mantenimento) riduce in maniera significativa il numero di recidive (a 7-12 mesi) e il numero di ricoveri nei pazienti con schizofrenia, rispetto al placebo (dati derivanti da un'analisi combinata di 65 trial clinici) (da Leucht et al., 2012, mod.)* [10].

drugs. In general, typical antipsychotics tend to have more motor effects, while several atypical antipsychotics can cause metabolic adverse effects; all first-generation antipsychotics and most second-generation antipsychotics can cause hyperprolactinaemia, with the exception of aripiprazole, clozapine and quetiapine. Motor symptoms influence movement and muscular tone and can lead to Parkinsonism (tremor and muscular rigidity) and muscle spasms (dystonia) as well as subjective and objective restlessness (akathisia). These symptoms are known collectively as acute extrapyramidal symptoms (EPS). Another EPS, which usually appears late in the course of treatment together with aging of the patient, is tardive dyskinesia, a symptom characterised by involuntary and repetitive movements of the limbs, trunk and more characteristically of the libs, tongue and jaw. Metabolic disorders include weight gain and changes in blood glucose, cholesterol and other lipids. These disorders can negatively influence the physical health of patients with schizophrenia. Other hormonal disorders, and in particular an increase in the levels of prolactin, can give rise to secondary problems such as sexual dysfunction.

Adherence to antipsychotic therapy is often low in persons with schizophrenia [5]: about 50% of patients are non-adherent to oral therapy [19], even if this percentage is higher in long-term studies. The main reasons for low adherence include:

- lack of information about the disease and its treatment;
- lack of improvement of psychotic symptoms;
- adverse effects (that resolve if the patient interrupts therapy);
- lack of knowledge about the need for treatment;
- economic difficulties (especially in countries in economic difficulty);
- complexity of treatment schemes;
- fear of discrimination;
- poor physician-patient relationship;
- lack of support by caregivers.

The lack of adherence to therapy is commonly associated with relapse, which often leads to hospitalisation; however, the association between adherence and hospitalisation can also depend on the fact that lack of adherence may represent a symptom of progression of disease [20]. The frequency of hospitalisation (often used as an indicator of severe relapse) is up to 400% higher in non-adherent patients than those who are adherent to therapy [21]. Moreover, non-adherent individuals have a greater probability of low overall function in the long term and to be

TABLE II.
Potential side effects of current antipsychotic medication (from Fleischhacker et al., 2014, modified) [1]. *Possibili effetti collaterali degli attuali farmaci antipsicotici (da Fleischhacker et al., 2014, mod.)* [1].

• Extrapyramidal symptoms – Slow, stiff movement and tremor (parkinsonism) – Abnormal muscle tone/muscle spasms (dystonia) – Involuntary movements (tardive dyskinesia) – Subjective experience of restlessness and restless movements (akathisia)
• Weight gain
• Metabolic disturbances – Changes in blood glucose levels – Increases in cholesterol and triglycerides
• Sedation
• A feeling of being ill-at-ease (dysphoria)
• Hormonal changes
• Sexual dysfunction
• Changes in the electrical activity of the heart (rare)
• Neuroleptic malignant syndrome (a rare but life-threatening neurological disorder)
• Agranulocytosis (very low levels of white blood cells, also life-threatening but rare)

more violent and attempt suicide more frequently than patients who are adherent to therapy.

Adherence to antipsychotic therapy can be improved through better understanding of the individual motivations for the lack of adherence and involving the patient in treatment decisions. One possible obstacle to adherence is the common practice of using polytherapy to control symptoms, which renders it difficult for patients to remember when to take various medications. Polytherapy, whenever possible, should be avoided. In addition, the use of long-lasting injectable formulations (depot) of antipsychotics may be associated with better adherence [22].

An individualised approach to therapy should be encouraged, which should also include patient preferences [1]. Drugs with tolerability and safety profiles that are adequate to the needs of the patient should be chosen (e.g., avoiding drugs that lead to weight gain if this represents a problem). Weight gain can be a significant problem in younger patients. About 25% of patients with a new diagnosis of schizophrenia are less than 18 years of age and can be particularly sensitive to side effects such as weight gain or menstrual cycle disorders associated with drug-induced hormonal changes. Careful and frequent monitoring of adverse effects should be carried out in all patients undergoing long-term therapy.

Antipsychotics are effective in reducing psychotic symptoms, but many patients show only partial response to treatment [3]. Even when patients obtain remission, few are completely free of symptoms. Moreover, up to one-third of patients affected by schizophrenia show a poor response to antipsychotics, and some develop resistance to treatment. Treatment resistance generally occurs with disease progression [23], but in about 10% of cases it is already evident after the first episode [19].

Psychosocial therapies

In addition to pharmacological therapy, psychosocial therapy also plays an important role in treatment of schizophrenia [1 24 25]. These therapies have the aim of improving the functioning of the patient in the community, which can also lead to clinical improvement, such as a reduction in the number of relapses or hospitalisations. The use of psychosocial therapies is supported by substantial evidence; these include cognitive behavioural therapy (CBT) for psychosis, in addition to cognitive remediation and functional skills training; other approaches also appear promising (Tables III, IV) [1 24 25]. Schizophrenia associated disabilities often involve several areas, and psychosocial therapies can be combined to confront a range of problems. For example, social skills training can be used as part of an integrated program that includes family psychoeducation, cognitive remediation and CBT.

Assertive community treatment

Assertive community treatment (ACT) is a model that was developed to improve the rate of relapse and hospitalisation following the transition from institutionalisation to territorial care in the USA starting in the 1980s [25]. This approach, aimed at a subgroup of patients who are strong users of services, involves a multidisciplinary team working in the community to provide a range of services comprising management of pharmacological therapy, practical support (e.g. housing) and rehabilitation. ACT is characterised by a high frequency of outpatient visits and a low number of patients (usually about 10) who are followed by each member of the team: these two characteristics obviously require considerable resources, even if it has been demonstrated that, for treatment of schizophrenia as for other psychological therapies, an increase in the time spent with the patient can contribute to achieving positive results [24 25]. Studies in several countries have demonstrated that ACT is associated with a lower incidence of homelessness and hospitalisation compared with standard care in patients who are frequent users of services [24-26]. One analysis revealed that, on average, there is a reduction in homelessness by 37% in patients undergoing ACT compared with standard care [26]. Even if ACT can help individuals with schizophrenia to live a stable life in the community, several studies have suggested that it has a relatively limited impact on other outcomes such as social functioning or employment. Recently, the OPUS study [27], carried out on patients with a first episode of schizophrenia, showed that ACT was superior to standard therapy in reducing both positive and negative symptoms and substance abuse, increasing overall patient satisfaction and adherence to therapy and in reducing the number of hospitalisations.

Cognitive-behavioural therapy

Psychotic symptoms can persist despite antipsychotic medications, which constitute a large obstacle to social recovery. CBT (a *talking* therapy that helps people manage their disease by changing their way of thinking and listening) directed towards psychotic symptoms aims to reduce their severity and consequent distress [24 25]. Many studies have demonstrated that this approach improves social functioning, reduces positive and negative symptoms and decreases mood disorders *vs* a control group. Other studies, however, have not demonstrated such improvements, and the effects of CBT on outcomes such as hospitalisation, depression, suicidal tendency and insight have not been clearly established [28]. A recent systematic review concluded that CBT does not offer a clear advantage over other psychosocial therapies such as family therapy and psychoeducation [29]. Evidence supporting the use of CBT is largely shown by studies in which partici-

TABLE III.
Many psychosocial interventions have been shown to improve outcomes in schizophrenia (evidence-based approaches), and others are being developed and evaluated (promising approaches) (from Fleischhacker et al., 2014, modified) [1]. *Molti interventi psicosociali hanno dimostrato di migliorare l'outcome nella schizofrenia (approcci evidence-based) e altri sono in fase di sviluppo e di valutazione (approcci promettenti) (da Fleischhacker et al., 2014, mod.)* [1].

Evidence-based approaches	Promising approaches
• Assertive community treatment	• Cognitive adaptive therapy
• Cognitive behavioural therapy for psychosis	• Healthy lifestyle intervention
• Cognitive remediation	• Interventions targeting older individuals
• Family therapy/psychoeducation	• Prodromal stage intervention
• Peer support and self-help strategies	• Social cognition training
• Social skills training	• Social rehabilitation (Clubhouse Model)
• Supported employment	
• Integrated treatment for coexisting substance abuse disorder	

TABLE IV.
Potential benefits of psychosocial therapies (from Fleischhacker et al., 2014, modified) [1]. *Possibili benefici delle terapie psicosociali (da Fleischhacker et al., 2014, mod.)* [1].

Intervention	Potential benefits
• Assertive community treatment	• Reduction in rates of homelessness and length of hospital stays
• Cognitive behavioural therapy for psychosis	• Decreases in both positive and negative symptoms and mood disturbances, and improved social functioning
• First episode intervention for psychosis	• Improvements in quality of life, social functioning and adherence
• Cognitive remediation	• Improvements in cognition and psychosocial functioning
• Family psychoeducation	• Some improvement in social functioning and family coping and empowerment
• Peer support and illness self-management training	• Enhancement of empowerment and ability to cope with the illness
• Social skills training	• Improvements in social functioning
• Supported employment	• Increases in employment rates, hours worked and wages earned. Gains in self-esteem and quality of life
• Integrated treatment for coexisting substance abuse disorder	• Reductions in substance use and arrests; improved functioning

pants received at least 16 sessions [6]: CBT requires specialist training and experience, and thus cost is an important consideration. An analysis by the National Institute for Health and Care Excellence (NICE), however, concluded that CBT likely has a good cost-efficacy ratio, since the costs are compensated by a decrease in hospitalisation [6].

Cognitive remediation

Cognitive remediation programs usually utilise exercises aimed at improving aspects related to cognitive function, often combined with teaching strategies to improve the results of such exercises; these can also include different ways to limit cognitive deterioration [24 25]. The majority of studies have revealed that this approach is effective in improving cognitive function, while its effects on psychosocial functioning have been quite variable [24 25]. Models for cognitive remediation differ greatly and the number of reliable studies in this area is rather limited. It has been suggested that cognitive remediation augments the effects of other types of psychotherapy and improves the capacity to learn new abilities. Moreover, there is very limited evidence that its use for 2 years is associated with a reduction in the loss of cerebral grey matter correlated with schizophrenia [30] and an increase in the number of connections between brain cells and functional networks [31]. In a meta-analysis on over 2000

patients, [32] a long-lasting, mild-moderate effect of cognitive remediation was seen on cognitive function and on overall functioning that did not depend on the methodology of the study (type of approach, duration, etc.). Cognitive remediation was more effective when patients were clinically stable, and greater significant differences were seen on functioning when cognitive remediation was carried out in combination with other forms of psychiatric rehabilitation [32].

Family psychoeducation

Many persons with schizophrenia live with their families, and as such family intervention (also known as family psychoeducation in the USA) can play an important role in care [24 25]. Education of patients and families about the nature of schizophrenia and the symptoms of the disease helps them to develop coping strategies, capitalise on their strengths and learn to take better care of oneself. Patients (and their families) treated with family intervention are better able to participate in shared decisional processes. Family psychoeducation offers a valuable opportunity for persons with schizophrenia, their families and healthcare providers to exchange their personal experiences about the disease and its treatment. It is important to highlight that family members can provide a continuity of care for persons with schizophrenia, even if the healthcare operators involved in treatment change over time. A psychoeducational approach aims to promote collaboration between the family and healthcare providers. Studies have consistently shown that psychoeducational approaches are effective in reducing the rates of relapse and hospitalisation and in improving social functioning [24 25]. There is also evidence that these benefits are long-lasting (> 5 years) [33]. Since according to other studies the effects of family psychoeducation tend to subside after about 2 years due to an extinguishing effect, it has been suggested that 'recall sessions' in a multifamily setting may be useful in reducing the economic impact [34]. An initial analysis demonstrated that relapse and hospitalisations can be reduced by about 20% when family members are included in treatment compared to traditional care [35]. In another study, the rate of relapse at 2 years was 40% in patients in whom families received psychotherapeutic intervention and 75% when families did not receive any intervention [36]. The greatest advantages of family psychoeducation seem to be present in persons with a first episode of psychosis or recent onset of schizophrenia. Moreover, the benefits of psychoeducation also extended to family members who referred reduced levels of stress, better family relationships and greater ability to cope with problems and responsibilities [28].

Group multifamily psychoeducation is another useful intervention based on the family. In this model, qualified personnel guide a group of individuals with schizophrenia and their families who are given information about the course of disease and treatment of psychotic disorders. Participants also undergo problem-solving exercises that are designed to specifically help them to deal with the difficulties associated with care of a person with a psychotic disorder [37]. A multifamily approach can significantly reduce the rates of relapse compared with monofamily psychoeducation, which already reduces the rates of relapse *vs* treatment with no family psychoeducation (Fig. 2) [38]. Moreover, the addition of multifamily group psychoeducation to therapy with antipsychotics doubles the effects of pharmacological therapy alone [38].

Paradoxically, however, providing information can increase self-stigma of persons with schizophrenia, inducing them to expect prejudice and discrimination. The potential impact of self-stigma is shown in the International Study of Discrimination and Stigma Outcomes, an international study carried out in 27 countries in which 64% of participants referred that they no longer looked for employment, training, or education, and almost 75% said they felt the need to hide their diagnosis because of predictable discrimination [39]. However, in the long-term, psychoeducation – supported by adequate antipsychotic and psychosocial therapies – seems to be effective in reducing the burden experienced by many people with schizophrenia and their families [28].

Mutual support and self-help strategies

Persons with schizophrenia and their caregivers have noteworthy and accurate comprehension of the problems

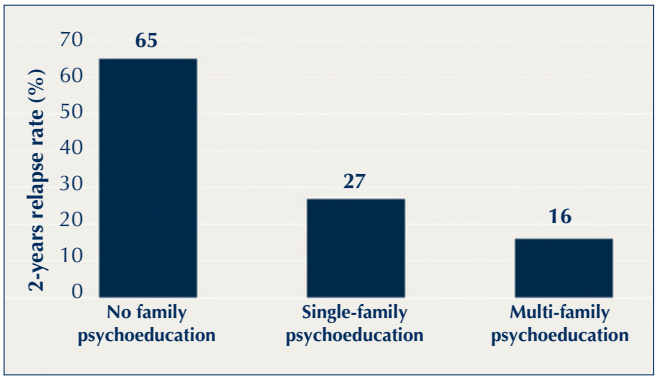


FIGURE 2.
Family psychoeducation reduces schizophrenia relapse rates, compared with treatment without family psychoeducation, and multifamily group psychoeducation is particularly effective (from Fiorillo et al., 2011, modified) [34]. *La psicoeducazione familiare riduce la percentuale di recidive di schizofrenia rispetto al trattamento senza psicoeducazione familiare, e la psicoeducazione multifamiliare di gruppo è particolarmente efficace (da Fiorillo et al., 2011, mod.)* [34].

associated with the disease. As a consequence, mutual support interventions can have an important role in the management of schizophrenia; this type of approach has been actively promoted in the USA and UK [40]. Mutual support groups, such as the National Alliance on Mental Illness (NAMI), the European Federation of Associations of Families of People with Mental Illness (EUFAMI) and the GAMIAN-Europe work together for affected individuals and caregivers. These groups can provide support in a number of different areas [40]. While peer-to-peer counselling seems to be useful when included as part of routine care, a self-help approach is generally more effective in other contexts (e.g., alcohol abuse or weight control) than in schizophrenia. However, in a recent report by the Schizophrenia Commission in the UK, 48% of patients with schizophrenia identified a self-help strategy as an important part of individual care [41]. There is also some evidence that self-help strategies can be useful in delaying hospital readmission, even if one study found no difference in clinical or social outcomes between individuals who participated in self-help groups compared with those who did not [42].

Social skills training

In persons with schizophrenia, problems in psychosocial functioning are related to disabilities in social skills that may be present before the onset of disease and persist if they are not addressed [24 25]. Social skills training can improve social proficiency, daily life, community functioning and other aspects of social functioning. The approach also has a small but significant effect on relapse [43]. The value of social skills training can be limited in some way to cognitive dysfunction in persons with schizophrenia [43]; however, its integration with cognitive remediation programs (or strategies aimed at improving attention and cognitive capacity), seem to be useful in improving the acquisition of social skills in patients with schizophrenia [44-46].

Supported employment

Schizophrenia can significantly reduce the ability of a person to work: on average, only 10-20% of persons affected with schizophrenia participate in the competitive workplace [24 25]. Persons with severe mental disorders such as schizophrenia are 6-7 times more likely to be unemployed than those without such disorders [47]. Data from the UK suggest that only 8% of persons with schizophrenia are employed, despite evidence that many would like to work [48]. Supported employment approaches can help persons with schizophrenia to obtain competitive employment, work longer and have higher salaries than persons without such support [26]. At least 50% of individuals who receive supported employment obtain a competitive job according to most studies [28]. The principal characteristics of such interventions are: focus on competitive employment; rapid search for work rather than a lengthy work training program; integration of psychiatric and employment services; emphasis on individual work preferences; continuous support in the workplace.

One of the most utilised supported employment models is Individual Placement and Support (IPS), according to which the only criterion for admission is the desire of the person to have a competitive job. The IPS model can produce notable savings in both social and healthcare costs, as well as potential benefits for the individual in terms of fewer hospital admissions and increased rates of employment [49]. Supported employment, however, has not been clearly demonstrated to improve long-term employment and economic independence in patients with schizophrenia. For this reason, it has been suggested that these strategies be adequately integrated with interventions such as CBT, cognitive remediation and social skills training [28].

Even if access to employment has a positive impact on mental health, the right type of employment must be considered: workplaces with low overall quality can cause stress, which can lead to psychological problems [47]. This is an important point since employers often have low expectations of persons with schizophrenia, and thus sometimes believe these individuals can only carry out jobs requiring low skill sets or with limited responsibility, or only volunteer work [48]. Retribution of work can be useful for persons with schizophrenia, even if this carries the additional risk of interrupting routine and consolidated habits.

Limitations of psychosocial therapy

Psychosocial therapy has some limitations that cannot be appreciated if symptoms are not well controlled and patients are not aware of their condition and the need to treat it. Involving the patient in the choice of treatment, for example, can be important in achieving a positive outcome: individuals who are highly motivated generally respond better to cognitive remediation than those who are less motivated [50]. Moreover, some persons affected with schizophrenia, if not treated with antipsychotics, can worsen when subjected to psychosocial interventions [51]. The costs of some therapies, such as CBT, can be prohibitive in countries in which adequate public healthcare resources are not available.

The design of studies aimed at investigating the efficacy of psychosocial therapies is not always as robust as the methodology applied to clinical studies for authorisation of a new drug. Thus, precisely planned, randomised controlled studies with adequate enrolment are needed in order to make strict recommendations regarding the use of these treatments.

Individualisation of treatment in schizophrenia

A. Rossi

Introduction

In spite of significant progress in understanding the nature of the disease, schizophrenia remains a challenging condition to treat. Schizophrenia is characterised by high morbidity and mortality: available treatments are inadequate, with variable efficacy, and are associated with several adverse effects. In spite of these obstacles, however, the availability of a wide range of individualised treatments, rehabilitative services and social support can effectively promote recovery of persons with schizophrenia [52] (Fig. 3). In reality, even if current antipsychotic treatments are not completely sufficient, they can nonetheless significantly reduce the burden of disease and improve daily life of patients. Towards this end, critical evaluation of the considerable amount of available information on antipsychotics and their individualised use is essential, and further efforts are needed to answer clinically important questions [53-57]. In clinical practice, decisions about the best antipsychotic with which to initiate treatment – or switch to another following treatment failure – is essentially an empirical process, since there is a limited amount of data in this regard on guiding treatment choices. In fact, while it is believed that the available antipsychotics have an efficacy that is broadly similar in treatment of schizophrenia [5], they differ significantly in their adverse event profiles. Given the notable variability in the pharmacokinetics of drugs and response to treatment in individual patients, it is worthwhile highlighting that efficacy is generally equivalent between groups of patients, although this is not necessarily the case when considering the single patient. At present, it is not possible to predict which antipsychotic is optimal for any given patient. There is no drug or dose that is valid for all patients, even if it seems that there is a dose range for optimal efficacy. Decisions about the choice of antipsychotic often follow a process of trial and error that includes careful monitoring of response and adverse effects, prompt evaluation of the risk-benefit ratio and when needed prudent switch to another drug [56] (Table V).

In general, typical or first-generation antipsychotics are effective in improving positive symptoms, but often cause motor symptoms or EPS that can be irreversible in the case of tardive dyskinesia. The most recent atypical or second-generation antipsychotics can improve both positive and negative symptoms and are less frequently associated with EPS and tardive dyskinesia than first-generation agents. However, weight gain, metabolic alterations and cardiovascular effects are associated with some second-generation antipsychotics (clozapine, olanzapine, thioridazine, risperidone, quetiapine for weight gain and metabolic effects; ziprasidone for increasing the QTc interval) have caused significant concern (Tables VI-X).

In spite of the progress made in psychopharmacology, many patients with schizophrenia interrupt or switch antipsychotics for lack of efficacy and/or treatment-adverse events, and a large proportion of patients remain symptomatic despite treatment. Individualisation of pharmacological treatment in schizophrenia, in addition to clinical experience and patient preference, should be based on three types of objective data: 1) clinical factors predictive of response to therapy; 2) predictable adverse effects of therapy; 3) pharmacogenetic and pharmacogenomic data.

Clinico-demographic variables and prevalent clinical dimension as predictive factors of response to therapy

The factors that influence variability of response to therapy with antipsychotics have not been clarified, thus rendering it difficult to develop effective treatment strategies for individual patients. The identification of clinical factors associated with outcomes in the treatment of schizophrenia would be of significant advantage in clinical practice. In fact, early identification of patients with poor response would allow avoiding ineffective treatments and associated adverse effects. Moreover, since some predictive factors can be corrected for, their individuation could provide a specific objective for treatment. Lastly, better understanding of factors related to response to therapy could help to better comprehend the physiopathology of the disease. However, to date studies that have attempted to identify factors associated with response to therapy have been largely negative. Nonetheless, some clinico-demographic variables have been associated with pharmacological response, including sex, duration of disease and duration of untreated disease, age of onset, comorbidity with other psychiatric disorders and substance abuse [58].

In recent years, data have emerged that associate differences in clinical response to pharmacotherapy in relation to the prevalent clinical dimension of the patient. The available data indicate that the presence of prevalent positive symptoms is associated with good response to antipsychotic therapy. A recent study, for example, demonstrated that response to pharmacological treatment is directly proportional to the severity of positive symptoms, showing that psychotic symptoms respond better to medical therapy [59].

The negative dimension is more difficult to treat, and if prevalent, is associated with poor long-term prognosis [60]. Olanzapine, aripiprazole and risperidone are more effec-

tive than haloperidol in treating the negative symptoms of schizophrenia, confirming data on the greater efficacy of atypical antipsychotics on this dimension [61 62].

The severity of disorganised thought in patients with schizophrenia is associated with poor long-term prognosis [63]. Moreover, the prevalence of symptoms of disorganised thought in patients with schizophrenia is predictive of response to antipsychotic therapy [64]. Disorganised thought and the positive dimension respond better to treatment with neuroleptics, even if recent data have demonstrated that disorganised thought responds better to atypical antipsychotics [65].

One of the biggest problems in the treatment of schizophrenia is recovery or at least maintenance of cognitive function. It is known that the severity of cognitive deficits is one of the most important predictive factors in long-term outcomes in schizophrenic disorders [66]. The available data are in fair agreement in sustaining that new antipsychotics are more effective than neuroleptics on cognitive function in schizophrenia [67]. It is still unclear, however, to what degree the effects of second-generation antipsychotics have on the cognitive dimension in schizophrenia, and especially if there are statistically significant differences between second-generation agents [68]. Moreover, whether or not the effects of atypical antipsychotics on cognitive function are generalised or concentrated on specific areas is still debated [68].

There is limited information on correlations between depression and outcomes in patients with schizophrenia. The available data suggest that atypical antipsychotics are not only not inferior to first-generation antipsychotics in this regard [69], but that at least some (amisulpride, aripiprazole, clozapine, olanzapine and quetiapine) seem to be more effective in treatment of depression in schizophrenia [4].

The presence of aggressive impulses is strongly correlated with suicidal behaviour in patients with schizophrenia [70]. While aggression is well controlled even by typical antipsychotics, there is much evidence showing that atypical antipsychotics, and in particular clozapine, improve impulsive behaviour and especially self-harm [14].

Predictable adverse effects of therapy

Current guidelines [53 55] recommend that the safety profile of the drug is a critical factor in the choice of antipsychotic in patients with schizophrenia. In reality, adverse effects of antipsychotics are a crucial aspect of therapy since they are the major cause of discontinuation of therapy. Adverse effects, therefore, can complicate and un-

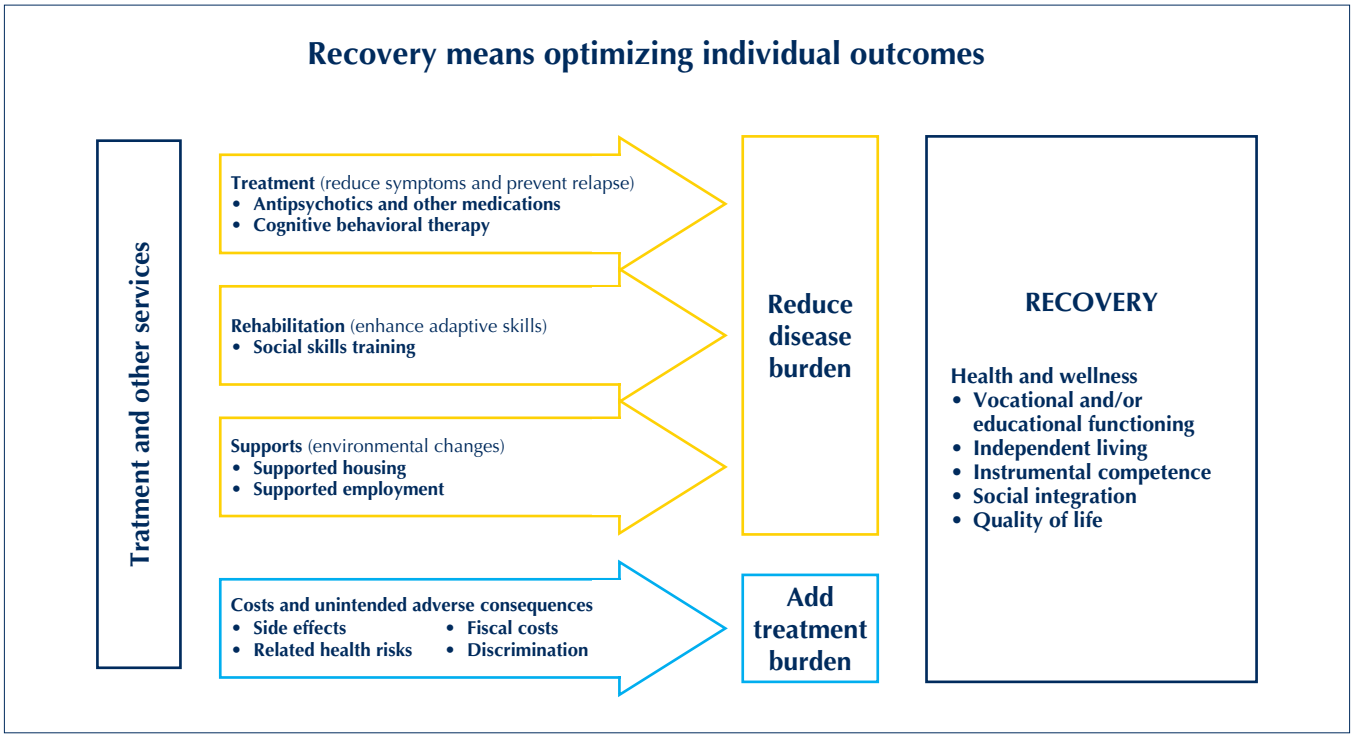


FIGURE 3.
Healing can be obtained by optimizing individual treatment (from Tandon et al., 2006, modified) [52]. *La guarigione può essere ottenuta ottimizzando il trattamento individuale (da Tandon et al., 2006, mod.)* [52].

TABLE V.
Steps to achieve optimum outcomes with currently available antipsychotics (from Bruijnzeel et al., 2014, modified) [56]. *Passaggi per ottenere un outcome ottimale con i farmaci antipsicotici attualmente disponibili (da Bruijnzeel et al., 2014, mod.)* [56].

1. Considerations in selecting the best antipsychotic for a particular patient
• Equivalent efficacy across agents
• Individual variability in response
• No good predictor of individual response to different agents
• Different agents have different side effects
• Different patients have different vulnerabilities and preferences
2. Proper antipsychotic trial sequence
• Begin with systematic 6-10 week trial of one antipsychotic with optimal dosing
• If inadequate response, follow with systematic trial of monotherapy with one or more other antipsychotics at adequate dose and duration
• If inadequate response, follow with a trial of clozapine or a long-acting antipsychotic
• Follow with a trial of clozapine, if not tried before
• Only then consider other strategies (e.g., antipsychotic polypharmacy)
3. Good practice guidelines for ongoing antipsychotic treatment
• Measurement-based individualized care
• Repeated assessment of efficacy using reliably defined treatment targets (facilitated by use of standard rating scales)
• Careful assessment of adverse effects
• Care consistent with health monitoring protocols
• Standard protocols customized to individual vulnerabilities/needs and specific agent
• Ongoing collaboration with patien tin decision-making

TABLE VI.
A summary of the first-generation and second-generation antipsychotic medications (from Xu Q, et al., 2013, modified) [81]. *Riassunto delle caratteristiche dei farmaci antipsicotici di prima e di seconda generazione (da Xu Q, et al., 2013, mod.)* [81].

	First-generation antipsychotic medications	Second-generation antipsychotic medications
Main content	Butyrophenones, phenothiazines thioxanthenes	Clozapine, olanzapine, risperidone, quetiapine, ziprasidone, etc.
Calming effect	Powerful	Weaker (except clozapine)
Receptor targets	Narrow, mainly D2 receptors	Multitarget, D2 receptors and serotonin receptors
High prolactin	Common	Less common(except risperidone)
Efficacy	Good	Equivalent or superior
Positive symptoms	Good efficacy	Good efficacy
Negative symptoms	Weaker efficacy	Better efficacy
Cognitive symptoms	Weaker efficacy	Better efficacy
Extrapyramidal symptoms	Serious	Light
Tardive dyskinesia	Common	Rare
Effective dose	Large dosage	Generally small
Compliance	Bad	Better
Weight gain	Obvious	More obvious(except ziprasidone)
Metabolic syndrome	Common, higher risk	Rare, lower risk

TABLE VII.
Recommendations for the antipsychotic treatment in the acute phase of schizophrenia (from Hasan et al., 2012, modified) [53].
Raccomandazioni per la scelta del farmaco antipsicotico nella fase acuta della schizofrenia (da Hasan et al., 2012, mod.) [53].

Antipsychotic agent	Category of evidence[a]	Recommendation[b]
Olanzapine	A	1
Quetiapine	A	1
Risperidone	A	1
Clozapine[1]	A	2
Haloperidol	A	2
Amisulpride	B	2
Aripiprazole	B	2
Ziprasidone	B	2
Asenapine[2]	F	–
Iloperidone[2]	F	–
Paliperidone[2]	F	–
Lurasidone[2]	F	–
Sertindole[2]	F	–
Zotepine[2]	F	–

[a] Category of evidence: Category of evidence where A = full evidence from controlled studies. [b] Safety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential. [1] Clozapine is highly effective in the treatment of first-episode patients, but because of its side effect profile it should be considered as recommendation grade 2. [2] It can be assumed that these antipsychotics are effective in the treatment of first-episode schizophrenia, but we could not identify any study to give an evidence-based recommendation.

TABLE VIII.
Recommendations for the antipsychotic treatment in relapse phase of schizophrenia (from Hasan et al., 2012, modified) [53].
Raccomandazioni per la scelta del farmaco antipsicotico nella recidiva della schizofrenia (da Hasan et al., 2012, mod.) [53].

Antipsychotic agent	Category of evidence[a]	Recommendation[b]
Amisulpride	A	1
Asenapine[1]	A	1/2
Aripiprazole	A	1
Clozapine[2]	A	1/2
Haloperidol	A	2
Iloperidone[1]	A	1/2
Olanzapine	A	1
Paliperidone[1]	A	1/2
Quetiapine	A	1
Risperidone	A	1
Sertindole[1,3]	A	1/2
Ziprasidone	A	1
Lurasidone	B	3
Zotepine	B	3

[a] Category of evidence: Category of evidence where A = full evidence from controlled studies. [b] Safety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential. [1] These drugs are not approved for the treatment of schizophrenia in all countries and therefore it should be generally considered as recommendation grade 2 in these countries. [2] Clozapine is highly effective in the treatment of multi-episode patients, but it is only recommended as second line treatment due to its special side-effect profile (see main text). [3] Sertindole has a safety rating of 1, but due to its cardiovascular side effect profile the use is restricted in some countries. In these countries, it should be considered as recommendation grade 2 for legal reasons.

dermine treatment with antipsychotics in various ways. In fact, adverse effects can cause or worsen the symptoms associated with schizophrenia, including positive, negative, cognitive symptoms and agitation, [71] and can also contribute to increased risk for other mental disorders [72]. Lastly, adverse effects are subjectively difficult to tolerate and can compromise the quality of life. Most adverse effects caused by antipsychotics are due to their action on neurotransmitter systems and anatomic regions that are different from those involved in their therapeutic effects [73]. Adverse effects are both class- and agent-specific and are often dose-related: these include neurological, cardiovascular, anticholinergic and antiadrenergic effects in addition to weight gain, metabolic disorders involving glucose and lipids and sexual dysfunction [53 73] (Table XI). Adequate treatment of adverse effects, especially during long-term treatment of schizophrenia, can affect adherence and therefore improve outcomes [74]. Neurological adverse effects such as EPS tend to be more frequently associated with typical antipsychotics, while metabolic effects (weight gain, hyperlipidaemia, diabetes) are more frequently associated with atypical antipsychotics [75]. In recent years, particular attention has been given to metabolic adverse effects, also because it has been demonstrated that metabolic syndrome is more common in patients with schizophrenia than in the general population. An alternative classification has been proposed for antipsychotics based on metabolic risk, in which they are divided in: a) antipsychotics with high metabolic risk (clozapine, olanzapine, thioridazine, risperidone, quetiapine); b) antipsychotics with low metabolic risk (ziprasidone, fluphenazine, haloperidol, aripiprazole, amisulpride). In particular, among atypical antipsychotics aripiprazole, ziprasidone and amisulpride have a neutral effect on weight gain and lipid metabolism, while aripiprazole and amisulpride do not increase the risk of developing type 2 diabetes [76].

TABLE IX.
Recommendations for the antipsychotic treatment of negative symptoms in schizophrenia (from Hasan et al., 2012, modified) [53].
Raccomandazioni per la scelta del farmaco antipsicotico nel trattamento dei sintomi negativi della schizofrenia (da Hasan et al., 2012, mod.) [53].

	Primary negative symptoms		Secondary negative symptoms	
Antipsychotic agent	**Category of evidence[a]**	**Recommendation[b]**	**Category of evidence[a]**	**Recommendation[b]**
Amisulpride	A	1	A	1
Asenapine[1]	F	–	B	3
Aripiprazole	C3	4	A	1
Clozapine	C3	4	A	1
Haloperidol[2]	F	–	A	1
Iloperidone	F	–	F	–
Lurasidone	F	–	B	3
Olanzapine	A	1	A	1
Paliperidone[1]	F	–	A	1
Quetiapine	B	3	A	1
Risperidone	F	–	A	1
Sertindole[1,3]	F	–	A	1/2
Ziprasidone	B	3	A	1
Zotepine	D	5	A	1

Primary negative symptoms are considered a core symptom of schizophrenia, whereas secondary negative symptoms are a consequence of positive symptoms (e.g. social withdrawal because paranoid ideas), depressive symptoms (e.g. post-psychotic of antipsychotic-induced depression) or environmental factors (e.g. social understimulation due to hospitalism) (Carpenter et al. 1985). [a] Category of evidence: Category of evidence where A = full evidence from controlled studies. [b] Safety rating = recommendation grade derived from categories of evidence and additional aspects of safety, tolerability, and interaction potential. [1] These drugs are not approved for the treatment of schizophrenia in all countries and therefore it should be generally considered as recommendation grade 2 or lower in these countries. [2] Haloperidol is the most commonly used FGA across all studies. Please see the main text for other FGAs. [3] Sertindole has a safety rating of 1, but due to its cardiovascular side effect profile the use is restricted in some countries. In these countries, it should be considered as recommendation grade 2 or lower for legal reasons.

Pharmacogenetic and pharmacogenomic data

The basis of individualised medicine consists in the presupposition that the unique characteristics of an individual have a significant role in the choice of the most appropriate therapy. Such characteristics include genetic alterations and epigenetic modifications, clinical symptoms, modification of biomarkers and environmental factors. The objectives of personalised medicine are to predict an individual's susceptibility to disease, obtain accurate diagnosis and determine efficacy and favourable response to treatment [77]. In particular, the aim of pharmacogenetics is to predict which patients will benefit from a certain drug based on genetic information in order to provide tailored treatment that will optimise reduction in symptoms and minimise adverse effects of the drug [78 79].

Pharmacogenetic studies are concentrated on the main pathways of molecules hypothesised to be involved in the mechanism of action (pharmacodynamics) and on enzymes that metabolise antipsychotics (pharmacokinetics). It is known since the 1960s that dysfunction of the dopaminergic system is at the basis of the physiopathology of schizophrenia. Dopamine has different subtypes of receptors (D1 to D5), but only D2, D3 and D4 have been extensively studied by pharmacogenetics [78 79]. In reality, a number of studies have evaluated the relationship between response to antipsychotic drugs and genetic variations in dopamine receptors. Another area of research involves the pharmacokinetics of antipsychotics, and in particular on the family of cytochrome P450 enzymes that metabolise most of these drugs. Variants in genes that code for these enzymes can lead to an increase or decrease in the metabolism of antipsychotics that can alter plasma levels of the drug. In the last 15 years, many variants of genes have been studied in relation to response to antipsychotic drugs [78 79]. The majority of pharmacogenetic studies on antipsychotics have investigated selected candidate genes, focusing on polymorphisms in genes that code for receptors of the dopamine and serotonin systems, in addition to genes that code for enzymes that metabolise antipsychotics such as COMT and CYP2D6 [78 79]. A number of phar-

TABLE X.
Choice of treatment in the acute phase of schizophrenia (from Lehman et al., 2004, modified) [54]. *Scelta del farmaco nella fase acuta della schizofrenia (da Lehman et al., 2004, mod.)* [54].

	Consider Medication From			
Patient profile	**Group 1: first-generation agents**	**Group 2: risperidone, olanzapine, quetiapine, ziprasidone, or aripiprazole**	**Group 3: clozapine**	**Group 4: long-acting injectable antipsychotic agents**
First episode		Yes		
Persistent suicidal ideation or behavior			Yes	
Persistent hostility and aggressive behavior			Yes	
Tardive dyskinesia		Yes; all group 2 drugs may not be equal their lower or no tardive dyskinesia liability	Yes	
History of sensitivity to extrapyramidal side effects		Yes, except higher doses of risperidone		
History of sensitivity to prolactin elevation		Yes, except risperidone		
History of sensitivity to weight gain, hyperglycemia, or hyperlipidemia		Ziprasidone or aripiprazole		
Repeated nonadherence to pharmacological treatment				Yes

macogenetic studies have attempted to identify genes that may be involved in inter-individual differences in adverse events induced by antipsychotics, although the results are inconsistent [78 79].

Pharmacogenetics involves the use of genomic techniques, such as genotyping, sequencing, gene expression, genetic epidemiology, transcriptome, proteomics, metabolome and bioinformatics to study drugs in clinical use, and apply high-throughput systemic approaches to accelerate the discovery of markers for response to therapy that may be related to the drug's target, its metabolism or course of disease [80 81]. Pharmacogenomics is different from pharmacogenetics as the former studies a wide range of genes that may be involved in the response to a drug, while the latter primarily examines specific candidate genes. For many drugs, interindividual differences are mainly due to single nucleotide polymorphisms (SNP) in genes that code for enzymes that metabolise or transport drugs and/or are targets of the drug (e.g. enzymes, receptors and defective proteins that alter metabolic pathways, leading to expression of the phenotype of the disease) [80].

The use of these techniques in disorders of the central nervous system is an extremely complicated process since the majority of neuropsychiatric disorders, including schizophrenia, are complex pathologies that involve many different genes. In addition, it is highly unlikely that a single pharmacological agent can reverse multifactorial mechanisms associated with neuronal dysfunction of most processes of the central nervous system with a complex phenotype that involves mood, personality, behaviour, cognition and functioning. Treating such a heterogeneous clinical picture generally requires the administration of a combination of diverse drugs [80].

Clinico-pharmacological management of the patient with schizophrenia

A. Fagiolini, A. Altamura, P. Rocca

Introduction

The discovery and development of antipsychotics started more than 50 years ago and has profoundly improved the quality of life of many patients with schizophrenia. As such, there is little doubt on the benefits (and disadvantages) of antipsychotics [82]. Antipsychotic drugs are generally recommended in all phases of schizophrenia, from treatment of acute episodes to prevention of relapse [83]. The important long-term objectives of treatment plans for schizophrenia include improving adherence to therapy,

TABLE XI.
Main side effects of typical and atypical antipsychotics (from Marder et al., 2004, modified) [73]. *Principali effetti collaterali degli antipsicotici tipici e atipici (da Marder et al., 2004, mod.)* [73].

Drug	EPS	Increased prolactin	Increased weight	Hyperglycemia	Hyperlipidemia	QTc prolongation	Sedation	Hypotension	Anticholinergic effects
Perfenazine	++	++	+	+(?)	+(?)		+	+	
Haloperidol	+++	+++	+				++		
Clozapine			+++	+++	+++		+++	+++	+++
Risperidone	+	+++	++	++	++	+	+	+	
Olanzapine			+++	+++	+++		+	+	++
Quetiapine			++	++	++		++	++	
Ziprasidone						++			
Aripiprazole							+*		

* Sedation is indicated with higher doses of therapeutic range.

rehabilitation through psychosocial interventions – that involve patients and often even family members – and improving the quality of life. A combination of antipsychotics with other types of intervention is very important in achieving these long-term objectives.
Several important questions regarding pharmacotherapy of schizophrenia – in particular when to initiate treatment and how long to continue it – are still unresolved and often lead to inadequacy of therapy for many patients (e.g. premature discontinuation or delayed access to pharmacological therapy) [82]. Poor adherence to pharmacological therapy is an important aspect that contributes to inadequate treatment [84]. Considerable efforts have been made to improve adherence by developing antipsychotics with better tolerability in formulations that enable prolonged administration of the drug, including long-acting injectables, also known as depot antipsychotics. In recent years, these formulations of atypical antipsychotics have shown promising results in clinical trials that have led to changes in attitudes towards these drugs, which were traditionally reserved for patients with recurrent poor adherence to treatment [82 85].

The continuity of treatment

In about 75% of cases, the course of schizophrenia is characterised by a remission phase that alternates with relapses; after the initial episode, it is estimated that only 14-20% of patients can completely recover [83]. Moreover, knowledge of the neurobiological bases of schizophrenia has provided evidence regarding the potentially progressive nature of the disease. There is clear evidence indicating that interruption of treatment is associated with relapse in the majority of cases [83]. In addition, it is increasingly evident that early treatment is associated with less destructive psychotic episodes, while delayed access to mental health services in recent onset schizophrenia seems to be associated with slower and incomplete recovery, increased risk of relapse and poorer prognosis. Continuity of treatment in the initial phases appears to be crucial and can modify long-term prognosis. A study by Robinson [64] clearly showed that in spite of a good overall response to initial treatment, patients with a first episode of schizophrenia had a rate of relapse that was > 80% at 5 years. Following initial remission, discontinuation of the antipsychotic was identified as a significant factor for relapse, increasing the risk by almost 5-fold.
To date only a few controlled clinical trials have evaluated the possibility of preventing relapse, which is seen in 41-79% of cases at 12 months after dose reduction or discontinuation of treatment [11] (Table XII) in patients with a first episode of schizophrenia. In one of these studies [86], 131 patients with a first episode in remission for at least 6 months were randomised to gradual discontinuation of therapy or to continue treatment, consisting in the majority of cases of low doses of antipsychotics, and followed for 18 months. Discontinuation of therapy was associated with a significantly higher rate of relapse (43% *vs* 21%, $p < 0.011$). A more recent randomised controlled trial [87] compared the efficacy of additional maintenance therapy to intermittent treatment in prevention of relapse in patients with a first episode of schizophrenia in remission and who had been on maintenance therapy for at least one year. The percentage of relapses was significantly higher in the group receiving intermittent treatment than in those undergoing continuous maintenance therapy. Both these trials further highlight the importance of continuous maintenance treatment in patients with a first episode, even after one year in remission.
In light of results that indicate the importance of continu-

TABLE XII.
Studies reporting symptom recurrence rates after treatment reduction/discontinuation after a single episode of psychosis (from Emsley et al., 2013, modified) [11]. *Studi che riportano le percentuali di recidiva dopo riduzione/sospensione del trattamento a seguito di un singolo episodio di psicosi (da Emsley et al., 2013, mod.) [11].*

Authors	Sample size	Treatment duration	Symptom recurrence rates					Comparator recurrence rate
			9 months	12 months	18 months	24 months	36 months	
Kane et al.	28	Not specified		41%				0%
Crow et al.	120	Not specified				62%		46%
Gitlin et al.	53	3 months in remission		78%		96%		-
Wunderink et al.	161	6 months in remission			43%			21%
Chen et al.	178	12 months +		79%				41%
Gaebel et al.	44	12 months		57%				4%
Boonstra et al.	20	12 months min remission	82%					12%
Emsley et al.	33	24 months		79%		94%	97%	-

ous early treatment, the question can then be asked if long-acting antipsychotics (LAI) should be used in first-episode schizophrenia; at present, there are only limited data to answer this question [88 89]. A two-year open-label study [90] in patients with a first episode of schizophrenia demonstrated that those assigned to long-acting risperidone had a significantly lower rate of relapse and better adherence than those treated with an oral formulation of risperidone. In another open-label study [91] on patients with schizophreniform disorder or schizophrenia at diagnosis, treatment for 2 years with risperidone LAI was associated with remission in 64% of patients.

Duration of therapy

An open question concerns the optimal means of ensuring continuity of treatment, and in particular for how long maintenance treatment should continue in patients with schizophrenia that is in remission [82]. On the basis of clinical evidence and studies demonstrating that a 5-year period following an acute episode represents the period in which patients are particularly susceptible to relapse, maintenance therapy should last for at least 2 to 5 years [92]. According to the guidelines of the Canadian Psychiatric Association [93], for treatment of a first psychotic episode antipsychotics should be continued for at least 2 years following the initial remission of symptoms, while a minimum of 5 years of stability without relapse and adequate functioning should be observed before considering gradual discontinuation of the antipsychotic over a period of 6-24 months [74].
As in the treatment of other chronic diseases, a relevant problem of long-term, continuous antipsychotic treatment is adverse effects. In addition to the well-known neurological adverse effects of antipsychotics, there is good evidence that some atypical antipsychotics are associated with adverse metabolic effects. Some studies in animal models have suggested that chronic exposure to antipsychotics can contribute to a reduction in the volume of cerebral tissue associated with the disease [94]. However, a study [95] carried out in patients with recent diagnosis showed that prolonged treatment with long-acting risperidone was associated with a stable volume of white matter, in contrast to a reduction in volume observed in patients treated with the oral formulation of risperidone; the study concluded that modification of adherence with long-acting risperidone may act differently on the process of myelinisation, which would explain the better prognosis associated with the long-acting formulation compared with the oral formulation.
It is thus clear that the risk-benefit ratio of long-term treatment should be carefully evaluated and that care must be taken in prescribing the lowest dose of antipsychotic for effective control of symptoms.

Adherence to treatment

One of the main factors that leads to inadequate treatment and early discontinuation is poor adherence to therapy [84]. In fact, poor adherence is one of the most important problems in treatment of patients with mental disorders. The majority of hospital admissions are due to non-adherence, even if it is often not clear if non-adher-

ence was the cause or consequence of relapse [96]. The percentage of patients that are partially or completely non-adherent to therapy has been estimated to be between 40% and 60% [97].
The factors that contribute to poor adherence to pharmacotherapy for schizophrenia are related to the patient (low insight, depression, substance abuse), treatment (adverse effects, poor efficacy, complexity of therapeutic regimen) and lack of support or therapeutic alliance with the medical team [82 98 99] (Table XIII). Some of these factors can be overcome by improving the strategies used to administer the drug, such as long-acting formulations. However, it should always be considered that for early recognition and intervention of poor adherence, better education of patients and training of healthcare providers is extremely important. Poor adherence has been identified as an important risk factor for relapse [84 100]. The use of LAI antipsychotics has been demonstrated to improve adherence to therapy, and is associated with fewer treatment discontinuations, relapses and hospitalisations [101].

Typical and atypical antipsychotics

Even if atypical antipsychotics are widely used, there is continued debate regarding their tolerability, which is presumed to be better than first-generation agents. In recent years, the propensity of atypical antipsychotics to induce weight gain and metabolic alterations in glucose and lipids has raised doubts about their advantages over typical antipsychotics. For this reason, the role of some atypical antipsychotics in treatment of schizophrenia has been reconsidered. Taken together, the results of recent analyses comparing typical and atypical antipsychotics has demonstrated a high level of heterogeneity between the two classes of drugs that does not allow for any general conclusions to be drawn. The choice of drug should thus be made on an individualised basis considering the available therapeutic options [53 74 83 102].

Long-acting injectable antipsychotics (LAI)

LAI antipsychotics were introduced over 40 years ago because of their numerous potential advantages over oral formulations, including the possibility to monitor compliance and distinguish poor adherence from lack of response, regular contact with the patient and caregiver, reduced risk of accidental or deliberate overdose, better bioavailability and more predictable correlation between dose and plasma levels [97].
However, LAI antipsychotics have several limitations such as slow dose titration, longer time to reach steady state levels and sustained adverse effects if discontinued for problems related to tolerability. Traditionally, LAI formulations are used in maintenance treatment of patients with schizophrenia, generally following clinical stabilisation with oral antipsychotics. LAI formulations of atypical antipsychotics have been developed for risperidone, olanzapine, paliperidone and, more recently, for aripiprazole: at present, there are 10 LAI formulations, 6 first-generation and 4 second-generation [103].
Even if it is reasonable to expect that LAI antipsychotics can improve adherence to therapy and clinical outcomes, the clinical evidence obtained over the years regarding such benefits is not entirely clear, while the analysis of more recently introduced LAI antipsychotics is in progress. A series of analyses and systematic reviews has been carried out to indirectly compare the efficacy of LAI antipsychotics with oral formulations of both typical and atypical antipsychotics [104-108].
A large systematic meta-review [104], covering 8 Cochrane reviews of randomised clinical trials of individual typical LAI antipsychotics in patients with schizophrenia or schizophreniform disorder showed that the rates of relapse and tolerability profiles are similar for oral and LAI formulations, while general clinical improvement was significantly higher for LAI compared with oral formulations.
A recent systematic review [105], including studies with different designs and comparing typical LAI antipsychotics with atypical oral formulations, indicated that the LAI antipsychotics had greater clinical benefit than oral formulations, although the results were variable and inconclusive mainly because of the heterogeneity in methods and interventions used in the various studies. In addition, a recent publication [109] confirmed that studies using different methodologies may give different results, and that studies on LAI antipsychotics may be an example of a situation where conventional randomised trials may not be the gold standard: in fact, these types of studies tend to increase adherence to treatment and therefore lead to underestimation of the possible benefits of LAI antipsychotics compared with the corresponding oral formulations. A significant reduction in the rates of relapse (21.6% *vs* 33.3%, RR 0.70, 95% CI 0.57-0.87, p = 0.0009) and dropouts for inefficacy of typical LAI antipsychotics compared to oral antipsychotics was reported in a systematic review and meta-analysis of 10 long-term RCT lasting at least 12 months published between 1975 and 2010, for a total of 1,700 outpatients [106].
Another systematic review of studies published between 2000 and 2011 [107] compared the efficacy of LAI and oral antipsychotics on relapse, hospitalisation and all-cause discontinuation of therapy in schizophrenia revealed a clear difference between observational studies (4 prospective and 4 retrospective), which showed a significant advantage for LAI formulations (prospective: RR = 0.62,

TABLE XIII.
Factors associated with non-adherence (from Kane et al., 2013, modified) [99]. *Fattori associati con la mancata aderenza (da Kane et al., 2013, mod.)* [99].

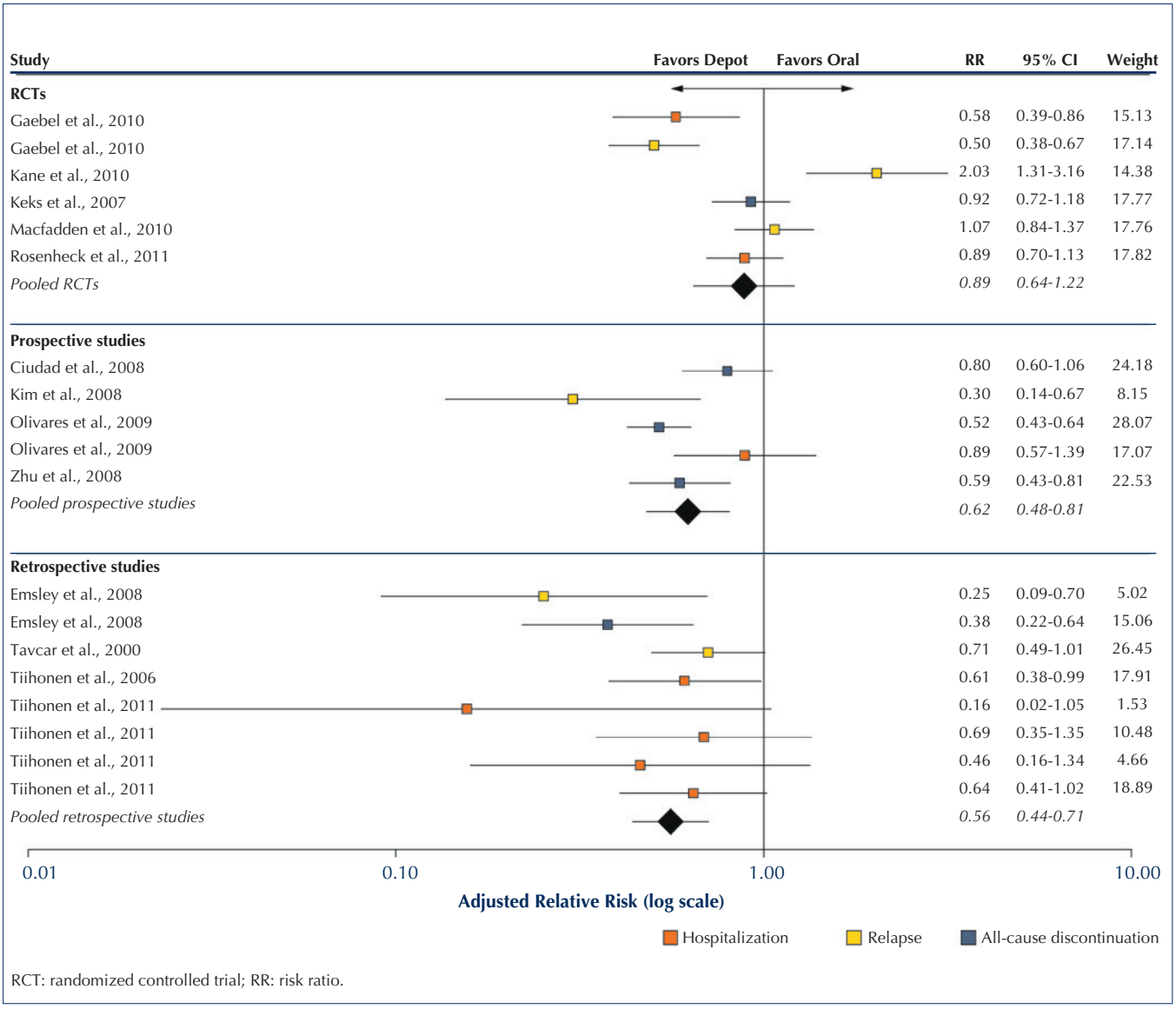
Patient characteristics	**Provider/system/treatment characteristics *(continued)***
Sex, age, race	Duration of treatment (past and expected)
Education	Complexity of administration
Socio-economic status	Accessibility and cohesion of services
Knowledge	Access to care
Perceived need for treatment (insight)	Continuity of care
Motivation	Reimbursement
Beliefs about treatment risks and benefits	Ability to monitor adherence
Past experiences/"transference"	Provision of psychoeducation
Past history of adherence	Availability of trained psychosocial treatment specialists
Self-stigma	Evaluation of obstacles to adherence
Illness characteristics	Access to alternative formulations (e.g., long-acting injectable antipsychotics)
Illness duration (first episode, chronic)	Complexity of administration
Illness phase (acute, maintenance, etc.)	
Symptom type and severity (e.g., negative symptoms, depression, demoralization)	**Family/caregiver characteristics**
Cognitive function	Nature of relationship
Lack of insight	Perceived need for treatment (insight)
Substance use	Beliefs about treatment risks and benefits
Comorbidities	Knowledge, beliefs, attribution
Degree of refractoriness	Involvement in psychoeducation
Potential for relatively asymptomatic intervals or "spontaneous remission"	Involvement in adherence monitoring
	Stigma
Medication characteristics	Environmental characteristics
Efficacy (consider different domains)	Physical environment
Effectiveness	Level of supervision
Adverse effects (of relevance for the patient)	Orderliness
Delivery systems/formulation	Safety and privacy
Dosage frequency	Stigma
Cost/access	Extrafamilial support system
Provider/system/treatment characteristics	**Other resource characteristics**
Therapeutic alliance	Financial
Frequency and nature of contact with clinicians	Transportation

95% CI 0.48-0.81, $p < 0.001$; retrospective: RR = 0.56, 95% CI 0.44-0.71, $p < 0.001$), and randomised controlled studies (5 trials), which showed a non-significant difference favouring LAI formulations (RR = 0.89, 95% CI 0.64-1.22, $p = 0.416$) (Fig. 4). The authors of this meta-analysis concluded that in this type of comparison the trial design can considerably influence the results, probably since controlled clinical studies, even if avoiding confounding factors and possible selection bias associated with observational studies, are not reflective of a real-world treatment setting.

A meta-analysis of 13 randomised trials on 6,313 patients [108] compared efficacy and safety of second-generation LAI antipsychotics to placebo and oral antipsychotics. It was found that LAI antipsychotics were more effective than placebo [$p < 0.001$ for PANSS (positive and negative syndrome scale) score] and at least as effective and safe than oral antipsychotics.

Efficacy and safety of individual LAI antipsychotics

For risperidone LAI, despite studies that have demonstrated significant reduction in relapse with LAI formulations over oral formulations, other studies have not confirmed this superiority [82 106 110 111]. It is likely that the differences in results are related to dissimilarities in the quality, design and methodologies of various studies [82].



RCT: randomized controlled trial; RR: risk ratio.

FIGURE 4.
Meta-analysis of adjusted risk ratios, by study design (from Kirson et al., 2013, modified) [107]. *Meta-analisi del rischio relativo standardizzato, a seconda del disegno dello studio (da Kirson et al., 2013, mod.)* [107].

The efficacy and tolerability of olanzapine LAI (olanzapine pamoate) has been investigated in two randomised, double-blind, studies, one versus placebo [112] and the other versus oral olanzapine [113]. In the former, olanzapine was found to be significantly more effective that placebo in reducing the PANNS score, but with weight gain and alterations in lipid metabolism. The second study demonstrated the efficacy of olanzapine LAI in maintenance treatment up to 24 weeks.

Several studies have demonstrated that paliperidone LAI (paliperidone palmitate) is more efficacious than placebo and is non-inferior to risperidone LAI in improving the PANSS score in patients with symptomatic acute schizophrenia or in delaying the appearance of relapse in patients with stable disease [114 115]. Paliperidone LAI has been demonstrated to have a metabolic profile similar to other second-generation antipsychotics; moreover, as in the case of olanzapine LAI and risperidone LAI, its use has been associated with worsening of psychosis in some patients [116].

More recently, the EMA has approved aripiprazole LAI for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole [117]. The clinical efficacy of aripiprazole LAI has been established in two

randomised, double-blind clinical studies in patients with schizophrenia. In the first [118], aripiprazole LAI was shown to be non-inferior to oral aripiprazole considering both the rate of relapse after 26 weeks and improvements in the PANSS score. In a previous study [119], aripiprazole LAI was associated with a risk of relapse at 52 weeks that was 5.03 fold lower than placebo. The most common adverse events observed in the two studies were: weight gain (9.0%), motor symptoms (7.9%), insomnia (5.8%) and injection site pain (5.1%). In particular, injections site reactions were generally mild to moderate and self-limiting; injections site pain appeared at a median of 2 days after injection and lasted for a median of 4 days. Aripiprazole LAI was associated with a greater frequency of EPS (18.4 %) than oral aripiprazole (11.7%); motor symptoms were the most frequent adverse effect and generally appeared around 10 days after the first injection and lasted for a median of 56 days, while Parkinsonism was slightly less frequent (6.9%). In the study by Fleischhacker [118], weight gain ≥7% *vs* baseline and last visit was 9.5% in the group treated with aripiprazole LAI and in 11.7% the oral aripiprazole group; weight loss ≥7% from baseline values to last visit was seen in 10.2% of patients treated with aripiprazole LAI and 4.5% of patients in the aripiprazole oral group. In a previous study by Kane [119], weight gain ≥ 7% was seen in 6.4% of patients treated with aripiprazole LAI and 5.2% of subjects in the placebo group; weight loss ≥ 7% was seen in 6.4% in the aripiprazole LAI group and 6.7% of patients in the placebo group; the mean change in weight from baseline to last visit was -0.2 kg for LAI and -0.4 kg for placebo (p = 0.812).

Quality of life, functioning and treatment satisfaction of patients with LAI antipsychotics

Quality of life is an important parameter in evaluating the benefits of treatment, especially in chronic diseases. Studies that have examined patients switching from an oral to LAI formulation of an antipsychotic have reported significant improvements in the quality of life, overall functioning and treatment satisfaction [101].

In one study, following unsatisfactory treatment with oral antipsychotics, 182 patients with schizophrenia were switched to a LAI antipsychotic for 6 months [120]. Compared to baseline, over the 6-month observation period significant improvement ($p < 0.05$) was seen in the PANSS score. Moreover, significant improvement ($p < 0.05$) was seen in Global Assessment of Functioning, health-related quality of life and patient satisfaction. The effects of LAI on functional improvements and quality of life were also evaluated in a placebo-

TABLE XIV.
Decision algorithm for choosing a long-acting antipsychotic based on treatment compliance predictors reported in the literature (from Rossi et al., 2012, modified) [124]. *Algoritmo decisionale per scegliere un antipsicotico LAI basandosi sui fattori predittivi di compliance al trattamento riportati in letteratura (da Rossi et al., 2012, mod.)* [124].

Good compliance		Poor compliance
Late	Age at onset	Young
Long	Lenght of illness	Short
Yes	Insight	No
Mild	Positive and negative symptoms	Severe
No	Drug abuse	Yes
Low	Percentage of relapse	High
Low	Frequency of hospitalizations	High
Oral	Ongoing therapy	Oral/depot
No	Previous depot	Yes
↓		↓
Evaluate patient's interest in taking depot treatment considering: • Insight of illness severity • Educational level • Therapeutic alliance • Possibility of sharing the therapeutic decision with the physician		Evaluate patient's interest in switching to atypical depot. Considering: • Severity of illness • Dosages of ongoing therapy • Efficacy profile of the depot

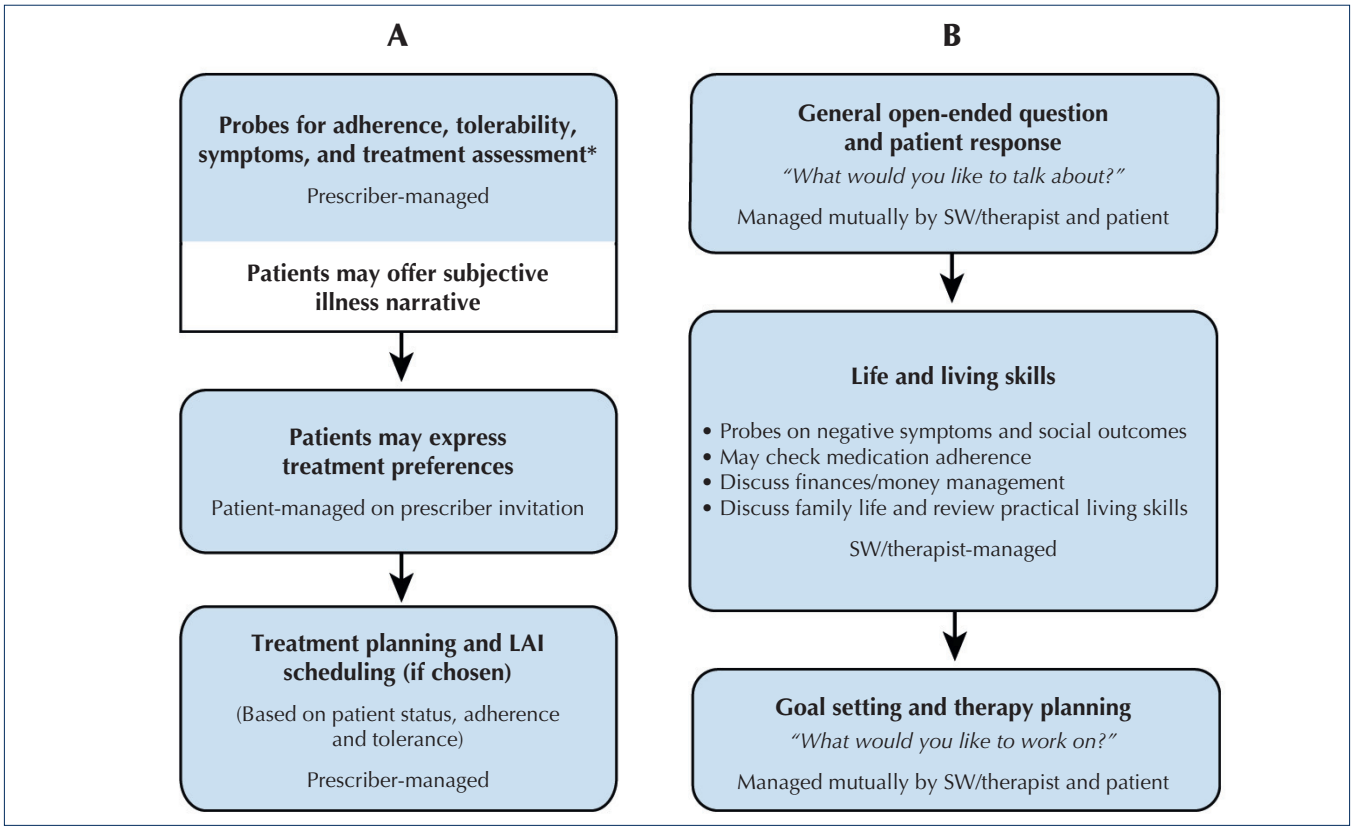


FIGURE 5.
Observed conversation flow between: A) patients and prescribers (n = 69); B) patients and social workers or therapists (from Potkin et al., 2013, modified) [128]. *Flusso di conversazione osservato tra: A) pazienti e prescrittori; B) pazienti e terapisti sociali (da Potkin et al., 2013, mod.)* [128].

controlled, randomised, double-blind, 8-week study on 404 outpatients with schizophrenia [121]. Significant ($p < 0.01$) improvement was seen with a LAI formulation compared to placebo in the quality of life and in the Short Form Health Survey. Macfadden et al. [122] assessed the efficacy of a LAI formulation on the quality of life and functioning in an observational, prospective 24-month study on 532 patients with schizophrenia. After initiation of therapy with a LAI, patients reported improvement at 3 months that continued throughout the 24-month follow-up period. Improvements were seen in Global Assessment of Functioning, Strauss-Carpenter Levels of Functioning, Personal and Social Performance and overall health. The Switch To Risperidone Microspheres trial [123] was carried out in patients with schizophrenia who were switched from an oral antipsychotic or first-generation LAI to a second-generation LAI for lack of efficacy, adverse effects, or poor adherence. After 6 months, improvements vs baseline were seen with the second-generation LAI for symptoms, global functioning, quality of life, treatment satisfaction and rate of hospitalisation.

Current uses and guidelines for LAI antipsychotics

Current guidelines [53 74 83 92 93] generally recommend LAI antipsychotics for maintenance therapy, among the other options for maintenance therapy, and/or when better adherence is needed. According to the guidelines, LAI can even be considered in the acute phase of schizophrenia if there is repeated lack of adherence or poor adherence [92 124], while the data on the use of new LAI formulations in patients with a first episode are considered to be too limited to allow any specific recommendations (Table XIV). However, many experts feel that the guidelines are too conservative and that the position of LAIs in treatment of schizophrenia should be reconsidered [96]. With the increase in information on the efficacy and tolerability of atypical LAI antipsychotics, international guidelines should be updated regarding the different phases of disease in which LAIs can be recommended and on the patients who could benefit from their administration.
Other data that has emerged from studies carried out in several Western countries, including Italy, concerns the

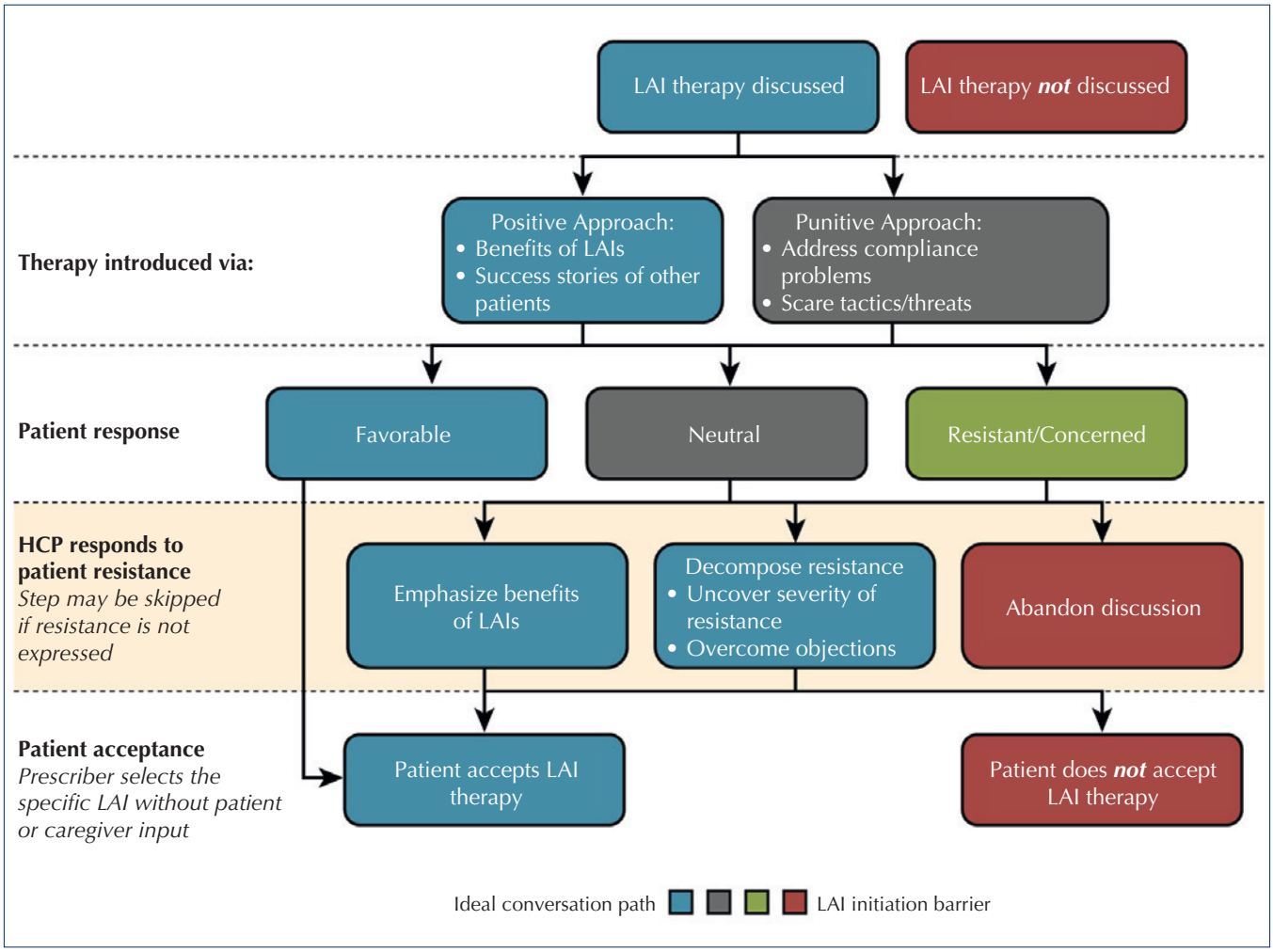


FIGURE 6.
Observed conversation decision tree for prescriber interactions with patients regarding initiation of long-acting injectable antipsychotics (from Potkin et al., 2013, modified) [128]. *Albero decisionale delle conversazioni osservate nelle interazioni con i pazienti riguardo all'inizio di una terapia con antipsicotici LAI (da Potkin et al., 2013, mod.)* [128].

relatively low use of LAIs even in patients who could clearly benefit from them. This can be explained by a number of misunderstandings and prejudices among prescribers, patients and caregivers for LAI formulations, which are considered older drugs, that are forced upon patients, reserved for those with poor adherence, and associated with adverse events and reduced involvement of healthcare personnel in the care of psychiatric patients [125]. Some psychiatrists consider LAIs as a 'last resource' of treatment, which should be used only when all other pharmacotherapies have failed, and reserved for patients who have presented with multiple episodes.
The high cost of LAI antipsychotics is another relevant barrier to increased prescribing of these formulations [106]. However, recent pharmacoeconomic studies have shown that atypical LAI antipsychotics can represent a favourable therapeutic strategy even from an economical standpoint.

Practical recommendations on the use of atypical LAI antipsychotics

There is broad consensus among specialists that the optimal use of new LAI formulations requires substantial changes in the general attitudes towards treatment with depot antipsychotics [82 96]. LAI antipsychotics should be utilised for any patient undergoing long-term treatment, and not only for those with problems in adherence [83 96 126]. Effective maintenance therapy can be considered as a starting point that leads to successful multimodal treatment programmes and rehabilitation. Since it is believed that oral antipsychotics should be initiated in patients with a new

diagnosis of schizophrenia [83], even if data on the efficacy of LAI antipsychotics are still limited, it can be expected that these formulations will also be favourable compared with oral antipsychotics in this setting. In patients with acute exacerbations of schizophrenia, in which the guidelines recommend treatment with oral antipsychotics, when the exacerbation is due to repeated non-adherence to poor adherence, the use of a LAI antipsychotic is advised [82]. Switching from an oral to LAI formulation requires precise strategies to maintain or improve therapeutic efficacy and minimise rebound cholinergic or histaminergic effects [127].

In conclusion, the recent development of LAI formulations of atypical antipsychotics has increased the number of treatment options for individualised treatment of schizophrenia, which is a fundamental aspect of management of patients with mental illness. Early intervention and continuity of treatment are key factors is achieving long-term remission, which prevents disruptive progression of disease and reduces the costs of the disease. The availability of new LAI formulations, with better tolerability in terms of EPS than typical depot antipsychotics, allows for the possibility to extend treatment with long-acting drugs, traditionally reserved for non-adherent patients with multiple episodes, to young patients in the initial phase of schizophrenia, who have a relevant risk of relapse if treatment is discontinued and the consequences of which would be devastating. Radical change in attitudes is needed among both physicians and patients to realise that long-acting antipsychotics can offer a new treatment paradigm: no longer ''last resort' drugs, but rather a potential first step towards continuity of treatment and clinical remission.

Two recent studies have confirmed this consideration. In the first, Potkin et al. [128] assessed the points of view of the patient and prescriber towards LAI antipsychotics by examining the conservations between patients and psychiatrists: the study revealed that the lack of information and dialog was often the basis for questionable choices, which excluded the possibility to consider the use of LAI antipsychotics even in cases for which they are clearly indicated (Figs. 5, 6). In the second study [129], negative attitudes and reluctance by many psychiatrists in prescribing LAI antipsychotics, and not patient resistance, was found to be the true cause of underuse of these formulations. In the future, we believe that well-designed long-term studies are needed to confirm the encouraging results obtained with atypical LAI antipsychotics.

Conflict of Interests

Carlo Altamura has received grant/research and/or has collaborated as consultant and/or speaker in symposia for Roche, Lundbeck, Merck, AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Sanofi, Eli Lilly, Pfizer and Otsuka.

Andrea Fagiolini has received grant/research and/or has collaborated as consultant and/or chairman and/or has participated as a speaker on symposia for Angelini, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen-Cilag, Lundbeck, Novartis, Otsuka, Pfizer, Roche.

Silvana Galderisi has received grant/research and/or has collaborated as consultant and/or speaker in symposia for Janssen-Cilag, Roche, Otsuka, Lundbeck, Pierre Fabre e Amgen-Dompé.

Paola Rocca has participated as speaker on symposia for Bristol-Myers Squibb, Janssen-Cilag, Otsuka, Roche.

Alessandro Rossi has received grant/research and/or has collaborated as consultant and/or speaker in symposia for Takeda, Roche, Lundbeck, Janssen-Cilag.

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"Continuum Care" in alcohol abuse disorders
A manifesto to bridge the gap in personalisation of treatment pathways

"Continuum Care" nei disturbi da uso di alcol
Un manifesto per colmare i gap nella personalizzazione dei percorsi di trattamento

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1. Alcohol: risks and prevention as a continuum

E. Scafato

Alcohol consumption is an important public health problem, and is responsible for 3.8% of all deaths in Europe and 4.6% of disability adjusted life years (DALYs). In Italy, it is estimated that about 8 million drinkers are at risk. Even if per capita consumption of ethanol in Italy has been significantly reduced to about 6.1 litres per year, heavy drinkers have not followed such a reduction. The WHO (World Health Organization) defines heavy drinkers as those whose mode of consumption causes damage to health (daily consumption of alcohol > 40 gm for women and > 60 gm for men).

Of the approximate 8 million consumers over the age of 11 years who are at risk in Italy, it is possible to reconstruct the increasing levels of consumption which, in a continuum starting from zero, are associated with increasing levels of risk, and in the case of persistent exposure organ damage may occur. In Italy, in 2012, about 400,000 men drank more than 5 drinks per day (1 drink is equivalent to 12 gm of alcohol). Over 220,000 are daily consumers considered harmful as they consume more than 3 drinks per day. As a consequence, it can be estimated that 620,000-720,000 individuals over the age of 11 years, who according to the WHO are not only at risk but considering clinically evident damage, are in close proximity to a profile suggestive of alcohol dependence (Fig. 1).

In the current situation in Italy, there is a substantial gap in education among physicians. Considering the level of exposition to risk in the Italian population, about 8 million consumers are at increased risk of which 10% already have organ damage or alcohol-related diseases. There is thus the objective need to guarantee a system that can utilise the existing network of expertise starting with primary health care through increased awareness and training for screening and early intervention of alcohol-related health risks. Such a system should benefit from the expertise of specialist services, which can assess the possibility to place individuals in specialist programmes for alcohol use disorders and indicate a possible course of treatment and rehabilitation. In diagnostic terms, the DSM-5 groups the harmful use of alcohol together with alcohol dependency, which reinforces the recommendations of the National Observatory for Alcohol of the CNESPS (*Centro Nazionale di Epidemiologia, Sorveglianza e Promozione della Salute*) regarding the need for increased services for alcohol use disorders. In 2012, a total of 69,770 individuals presented to services for alcohol use disorders. During the course of the last 6 years, no substantial changes have been noted regarding the type of clients (new client, current or recurrent user).

There are still about 620,000-720,000 individuals who should/could have sought medical services to receive assistance and/or treatment for problems caused by harmful consumption, suggestive of alcohol dependence or to slow the progression of damage and prevent alcohol-related complications. In fact, "only" 20,623 new alcohol-dependent individuals sought assistance for alcohol use disorders, in addition to the 49,147 alcoholics already under the care of the National Health System. This therefore suggests that there is a large imbalance between the number of clients observed and those expected on the basis of harmful consumption. Each year, no less than

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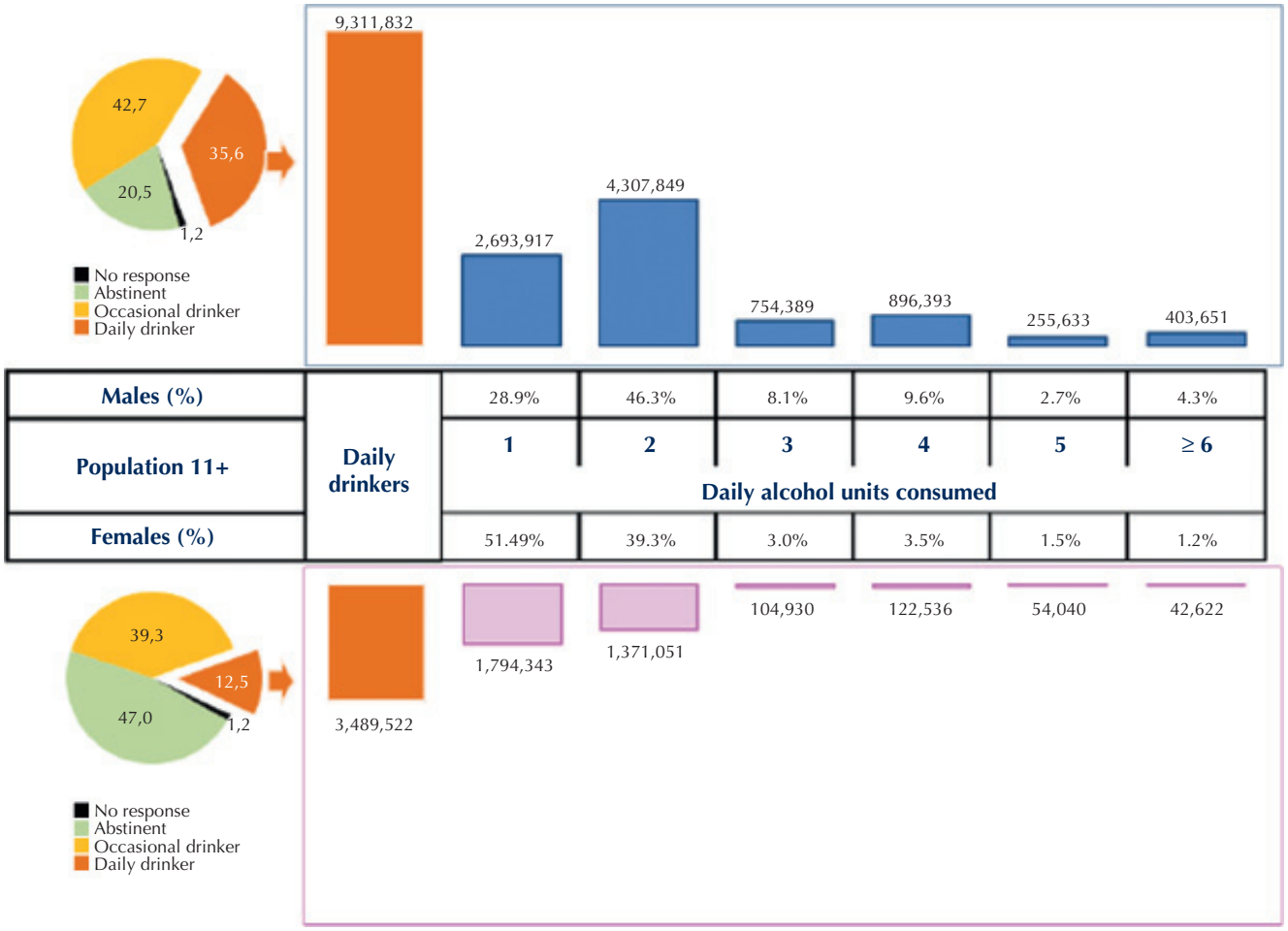

Source: ONA-CNESPS and WHO CC Research on Alcohol using data from the Italian National Institute of Statistics on the family, 2012.

FIGURE 1.
Distribution of alcohol consumption habits, 2012. *Distribuzione delle abitudini di consumo, anno 2012.*

5,000 new clients have constantly increased the number of clients with alcohol-related problems from 21,409 in 1996 to 69,770 (more than triple) who refer to structures within the National Health System (which have increased from 280 to 454, or a 62% increase). It should be pointed out that in recent years the number of personnel involved in services related to alcohol abuse has grown less compared with the considerable increase in clients.

It should thus be apparent that change is needed. A two-fold approach is needed that addresses both the high-risk population as well as consumers in the general population who are at increased risk. On one hand, the existing gap needs to be bridged between the number of expected alcoholics, those enrolled in alcohol abuse services and harmful consumers, increasing the proportion of individual identified, and to promote the emergence of alcohol use disorders as an unequivocal category, in order to halt progression of damage to health and prevent complications. In addition, initiatives aimed at raising awareness and promoting the elimination of social and health stigma, while favouring the ability of alcohol-related services to attract individuals with alcohol abuse problems for improved intervention and management.

Increased knowledge provides the necessary basis for renewed and more effective prevention and assistance, together with the optimisation of attitudes and adequate training of physicians in order to provide the prevention that is currently missing. The indispensible activity of greater integration in daily practice in Italy should not be limited to primary care, but extended to programmes

of early identification and intervention in other contexts. These include emergency departments, the workplace and social assistance through integration of good European practices as instruments of equity, accessibility and sustainability of the National Health System.
Considering that alcohol-related risk is a continuum in which it would be impossible to have knowledge of modifications in daily consumption or to move a person from a moderate risk category to a high-risk category of alcohol dependence, it would seem evident that the approach used for identification of risk and consequent management should be reconsidered. This is especially true considering that more than 69,000 alcohol-dependent individuals currently in alcohol use disorder services should be intercepted by a network of competencies that still need to be defined in order to obtain access to specialist care. To identify this 'underground' of individuals at high risk for alcohol dependence has value not only in health terms, but it also has a social and human impact. The access to treatment of alcohol-dependent individuals in Italy ranges between 12% of European estimates and 28% of the estimates of the Italian National Health Service. The proportion of individuals should be increased not only through increased availability and accessibility to adequate forms of treatment, but also through a renewed professional approach that favours sensitivity and the ability for early identification of at-risk individuals. This is also considering that increasing access to treatment to 40% of alcohol-dependent individuals would allow for a 13% reduction in mortality each year. At present, less than 30% of alcohol-dependent individuals attending alcohol use disorder services are receiving treatment, and the number of alcoholics in Italy is unknown, in contrast to other countries.
In summary:

- it is of fundamental importance to reconsider and renew approaches for prevention, early diagnosis and treatment of alcohol-related pathologies and problems. This includes the need to increase the number of individuals identified at healthcare structures through innovative programmes and better screening to favour access to treatment;
- there is an objective need to create a formalised network for early identification of alcohol-related risk that includes primary care physicians, hospitals and related services with the capacity for adequate case management;
- there is the need to reorganise services and working groups dedicated to alcohol dependence in order to unite the network of multiprofessional experts to ensure treatment with dignity;
- it is indispensible to formalise and guarantee early prevention and intervention in primary healthcare;
- it is crucial to favour integration of early identification and intervention in daily practice along with epidemiological monitoring;
- the risks associated with alcohol consumption and related damage to health must be adequately communicated to the general population.

2. Favouring access to treatment in alcohol abuse disorders: cultural, organisational and relational factors

M. Cibin

Alcohol is one of the most important risk factors for health and is a major cause of death and morbidity; notwithstanding, it Italy only about one-tenth of individuals with alcohol abuse disorders receive therapeutic intervention and specific rehabilitation. An evident criticism is thus accessibility to treatment, which is related in large part to the availability of first-line interventions. Once the patient has 'reached' treatment, the problem is posed of whether or not the treatment is adequate, which is correlated with the drop-out rate.
The 454 services or working groups on alcohol dependence in Italy have less than 70,000 clients, with a mean age of 45.9 years that decreases to 43.9 if only new entries are considered [1]. The majority of the increase in clients over the years is due to patients who remain in long-term treatment, while the number of new clients is relatively unchanged over time. The overall picture considering the available data is that of a heterogeneous system of intervention between different geographic areas in which it is difficult to recruit new patients, and in particular to recruit younger individuals with a short-lived history of alcohol abuse. Many services tend to maintain the current patient load and have difficulty in networking with other services, especially self-help groups.
Considering this background, there is a large number of subjects that need intervention for alcohol use disorders who do not have access to such interventions: it is estimated that at least 10-fold more individuals need intervention than those already receiving care.
The current situation is correlated with several heterogeneous factors:

- 'cultural' factors, stigmatisation;
- factors related to organisation of services;
- factors related to the setting of treatment programmes.

Regarding cultural factors, resistance to entry in treatment is related to personal and social stigmatisation: it is commonplace to view an alcoholic as a person who is marked, morally condemnable, severely marginalised and incurable, and there is also the widespread perception that treatment centres for dependency are receptacles of marginalisation and delinquency. The concept of alcohol use disorder as an 'accident' that could happen to anyone as a result of a risky lifestyle and/or traumatic events undoubtedly helps to overcome such

stigma, as does the awareness that the condition can be addressed and cared for with professional and scientifically validated tools. It is more difficult to deal with the stigma attached to treatment centres: these services are often located in degraded areas from both geographical and relational points of view. In addition, it should be highlighted that patients with alcohol-related problems can only rarely exercise their right to the choice of care, considering the territorial nature of centres for addiction and psychiatric services: cultural issues and factors related to the organisation of services acts synergistically to keep potential patients at a distance.

Among the organisational factors that hinder access of clients, the following should be considered:

a. distribution of services and availability of treatment, which is characterised by large heterogeneity between regions, especially between northern and southern regions;

b. approaches to organisation, which are dissimilar both at first contact (e.g. waiting times, fees) and overall setting of treatment programs. Specific pharmacological treatments are definitely underutilised, as are self-help groups and residential programmes.

For the purposes of access to treatment, however, the greatest shortcoming is the scarcity or lack of first-line interventions, which are by definition at the basis of effective management of any problem of epidemiological importance comparable to that of the alcohol use disorders. In terms of first-line intervention, both the general practitioner and specialists involved in treatment of alcohol-related pathologies (gastroenterologists, psychiatrists, neurologists) are fundamental. Current diagnostic and therapeutic tools can be used to propose efficacious interventions that are compatible in the setting of both the general practitioner and specialists, which can be carried out individually or through consultation with alcohol abuse services.

Other factors that can influence access and continuation of treatment are the setting of the programme, and in particular the relationship with the patient. This aspect is fundamental in order for the intervention to be efficacious and to reduce the possibility of early drop-out. As for any therapeutic intervention, this is of particular importance in the treatment of problems characterised by difficulty in motivational and decisional processes. Building a relationship, encouraging changes, supporting self-efficacy are all essential elements of a motivational approach, with the aim of defining together with patients the objectives and course of treatment.

While abstinence from alcohol use and other psychoactive substances would seem to be the most desirable goal, not all subjects have the motivation and personal resources to reach this endpoint. In some cases it is possible to define an objective of reduction, which will nonetheless minimise the dangerous effects of alcohol while reducing the possibility of drop-out. In the words of Alan Marlatt: 'If a client is ambivalent toward or resistant to changes, then harm reduction … gives us an opportunity to build a relationship and help our client make steps in the right direction … Reduction therapy means meeting the clients where they really are' [2].

3. Desirable *vs* achievable goals in intervention

A. Mosti

In alcohol abuse services, it is not infrequent, when faced with the ambivalence of patient who is seen for the first time, to ask: "Why did this person come to us if he is not motivated to face his problem? Is he not aware of the problems caused by his alcohol consumption? Why can't he 'admit' his condition even if his family brought him here? And, especially, if he doesn't want to completely stop drinking? Maybe he is only here to get a certificate for some reason, maybe to satisfy his spouse or to see what would happen once you cross the threshold of that strange place where 'they want you to stop drinking!' and see where your 'drinking buddies' have been".

In these circumstances, the tone of the first meeting can be decisive for engaging in a possible treatment aimed at improving the state of health and prevention of alcohol-related harm. One of the most common attitudes in the field of addictions has been to separate patients into 'motivated' or 'unmotivated'. In particular, an unmotivated person is usually challenged with a confrontational type session, characterised by emphasis on the negative aspects and the danger of the situation and on the negative consequences for the person in terms of health, family and social life, in addition to moral and legal problems associated with addiction. There is no doubt that individuals with addiction problems have serious problems with compliance, almost as if they 'do not want to heal'. At times, they seem to have full knowledge of their problems and, a moment later, may deny them. Faced with an 'unmotivated' person, who is so ambivalent, who pretends to want to change but who shows contradictory behaviour insisting that 'drinking isn't a problem, and that all considered it's true that sometimes he drinks too much – just like everyone – but in reality he can quit whenever he wants', approaches based on motivation for change seem to have opened a new horizons and provided effective operational tools such as the motivational interview [3].

In counselling relationships, according to the motivational interview, what the operator says should be able to elicit either a determined reaction or a reaction that is diametrically the opposite. This doesn't happen by chance. The operator carefully considers the position of the patient in an ideal process that ranges from lack

of motivation to change to full readiness to change [4]. In motivational interviewing, the tone of dialogue is based on listening to the person, on the total acceptance of the state of change in which the person is and on the level of commitment at that moment. Neglecting the conditions of the patient brings about a retreat to defensive positions with increasing resistance to change, and often to abandonment of the therapeutic relationship.

… there's always something to do …

In the spirit of the motivational interview, the operator should never say: "Or stop drinking now or there's nothing to do". Even at the stage defined as pre-contemplation, when the willingness to change is not maximal, because the patient does not even seem to have a perception of the problem, the operator should be empathetic and act as a relational reference point. At the same time, the operator should be careful to take advantage of occasions to evoke recognition of the problem and any concerns that the person brings in relation to it. There is a phase in which an attitude of ambivalence remains, which if accepted without reservation by the therapist can be used for the benefit of the patient and allow consolidation of decisional processes in the direction of change.

… I can't change you, but if you want I can help you to change …

One of the main principles of motivational interviewing is to 'enhance a sense of self-efficacy' and thus the 'confidence that people have in their ability to implement a predetermined behaviour, to achieve a specific goal in a specified time" [5]. Another basic characteristic of the motivational interviewing approach is autonomy: the operator supports the right and the ability of the patient's own self-determination and facilitates informed choices. On the other hand, no one except the interested person can change! Supporting the responsibility of decision means, in other words, to believe that people are able to decide for themselves.
In this light, what can represent a partial result for the operator (e.g. reduction of alcohol consumption rather than abstinence) is the only objective which is, for the patient, at this moment, possible. Working together to reach this goal can be decisive for consolidating the only indispensable condition for any programme of change: the therapeutic alliance.

4. The mutual aid group in providing a continuum of care

A. Baselice

The scientific literature and experience in the field have always highlighted the key role that self-help groups have in treatment of alcohol-related problems. The two largest organisations for mutual aid and for a scientific and multifamily approach in alcoholism are the 12-step programme (about 1000 groups in 12 countries; AA, Al-Anon, Al Ateen) [6] and the social-ecological approach (about 2000 groups; Club Alcologici Territoriali, CAT, Territorial Alcohol Clubs) [7]. These two types of non-institutional group interventions have a fundamental role within a collaborative relationship and are built with the network of public alcohol abuse services, both territorial and hospital-based. The goals of both types of intervention include: increasing the individual's ability to confront problems (empowerment) [8]; increasing self-esteem, skills and confidence in one's resources; help participants to express their emotions; stimulate reflection about one's behaviour; facilitate new friendships [9]. In these groups, confrontation and interpersonal sharing allows leaving behind egocentric behaviour and relational closure, and to re-establish intra/extra-family relationships [10]. The orientation is towards action 'here and now' in a group situation. Communication is horizontal and among equals. The level of interaction and responsibility are personal aspects [11]. Even if some of the founding principles and operating aspects are in common, the 12-step programme and the social-ecological approach have significant differences regarding some objectives and working methods. According to the social-ecological approach, alcoholism is a complex and multidimensional phenomemon produced by the bond between alcohol and man, and can be caused by bio-psycho-social disorders (complex alcohol-related problems) in an individual, family and even local community [7]. This premise is in complete harmony with the hypothesis of E. Morton Jellinek [12], according to whom 'alcoholism is any use of alcoholic beverages that provokes damage to the individual, society, or both'. Thus, alcoholism is a variable and complex disease phenomenon seen as an entity that can be attributed, from a nosographic standpoint, to an advanced and irreversible stage of the continuum of the relation between an individual and a substance and classified by the DSM-5 as 'Alcohol use disorder'.
The interaction between people from different types of families favours emotional re-elaboration that produces a consequent cognitive and behavioural redefinition. Such a change has its foundation in neuro-physiological neuro-plasticity, or the ability of the brain to change its structure in response to experience [13]. In this way, it is possible to develop effective coping strategies to confront craving and to develop a sense of self-efficacy in the search for motivation and possible maturation of an "alcohol/drug-free" behaviour towards an increasingly careful and profound reflection about the meaning of life [14].
The AICAT national database, realised in collaboration with the Institute of Clinical Physiology of the CNR at

Pisa during 2005-2006 showed that permanence of families with alcohol-related problems at the CAT (Territorial Alcohol Clubs) drastically reduced at-risk alcohol-related behaviour, and also led to an unmistakable reduction in other risky behaviour (illegal drugs, use of psychotropic dugs, and to some extent cigarette smoking). This demonstrates the enormous potential of the CAT (Territorial Alcohol Clubs) in facing many other problems that are not of lesser importance [15].

In light of these characteristics, over the last 15 years, the CAT (Territorial Alcohol Clubs) have in fact dissociated from the common types of mutual aid groups, while retaining some relevant elements. More than being a mere instrument of treatment, of outpatient or residential 'aftercare', the CAT (Territorial Alcohol Clubs) have experimented in early approaches to alcohol-related disorders that precede those diagnosed as advanced or serious, by anticipating and embodying a strategy according to a mode of continuum of care in alcohology [11].

In fact, an increasing number of individuals and families at CAT (Territorial Alcohol Clubs) present with a situation of pre-contemplation of an at-risk condition that is lower or less advanced. In these situations, the CAT (Territorial Alcohol Clubs) propose a course of research for motivation to change that requires time, that is not foreseeable or preventable, for maturation of choice and achievement of an alcohol-free state. The CAT (Territorial Alcohol Clubs) are increasingly a laboratory for best practice for protection and promotion of health and a better quality of life, even for those who do not consider themselves 'alcoholics', but who are concerned about their relationship with alcohol [16].

In this vast and complex horizon, the working methods of CAT (Territorial Alcohol Clubs) compare and interact, in a completely nonspiritual manner, with all possible pharmacological intervention protocols used to support a process of emancipation from alcohol-related suffering. The necessary synergy with specialised medical-pharmacological approaches, which are fundamental considering the increase in comorbidities, does not exclude the possibility to formulate critical judgement regarding pharmacological approaches that according to the social-ecological viewpoint do not favour emancipation from a condition of chemical dependence. Such a position arises from the awareness that it is not the drug, but the person, who is at the strategic centre of a process of maturation and resolution of the bond with alcohol, and overcoming a lifestyle related to it.

This is a vision that has scientific basis in new evidence offered by progresses in neuroscience demonstrating that neurobiology has a fundamental structural relation, and for this reason is based on the integration of the body, mind and brain [13]. The goal of this vision is not simply to attempt to reduce or remove symptoms because a patient does not fit a determined diagnostic classification. The aim is to provide tools to create a healthy life that is better integrated with oneself and with interpersonal relations, a well-being in the name of complete self-realisation [17].

5. The need to overcome the dichotomy "reduction of risky drinking-abstinence". The advantages of a philosophy of intervention that does not aim at immediate disengagement from alcohol

I. Maremmani

Among the various dichotomies that limit an effective approach to the problem of addiction, one of the most prominent is "integrated treatment versus reduction of damage". For years, these two strategies have been considered as opposite poles of different philosophies of intervention, one bound to the search for methods that lead the subject to complete abstinence, while the other prioritises a decrease in the use, with maximum reduction in the damage correlated with its use [18].

Supporters of harm reduction argue that this approach is desirable at any rate, promoting for each individual the opportunity to improve their health and reduce the risk of practices of abuse. Critics argue that this practice is useless as it does not intervene on the pathophysiology of the disease, maintaining the positive reinforcement of the intake of the drug and course of disease. If, however, these considerations are questionable for drugs, they cannot be applied to alcoholism. Sometimes the introduction of pharmacotherapy can facilitate the integration of these two different approaches to the problem [19].

Alcohol dependence remains an underdiagnosed and undertreated condition. The difficulty in treating subjects with at-risk drinking, but who are not yet severely alcohol dependent, is often the will of the subject himself, who does not want to immediately stop drinking even when he knows that a reduction in alcohol consumption is desirable.

The therapeutic agents used up to now have focused on pharmacologically-assisted detoxification of alcohol-dependent patients and long-term psychosocial treatment of detoxified subjects, or the use of drugs to prevent or delay relapse to alcohol in detoxified subjects. To date, no drug has been proposed to obtain a reduction in drinking. A reduction of alcohol intake in patients with alcohol use disorders can be considered an intermediate objective towards complete abstention in those at risk of physical and psychological complications in severe alcohol dependency (reduction of risk of disease progression and/or damage).

The process of acceptance of harm reduction in alcoholism begins with the following findings: alcohol

consumption, when high (> 1 unit in women and > 2 units in men), is one of the most important risk factors for disease; the risk of death increases with the alcohol intake in an exponential manner; at-risk drinking has negative consequences on the socio-environmental condition (decreased productivity, disruption of meaningful relationships, violent and criminal behaviour in the family and the social environments, increase in injuries), with an exponential trend that is related to alcohol intake.
Progressive increase of alcohol consumption is the greatest risk factor for alcohol dependence, which in turn is responsible for most psycho-physical complications and social issues related to drinking. Reducing the intake of alcohol means, therefore, to reduce the risk of developing addiction.
Reducing alcohol consumption has an immediate positive impact on the health of the at-risk drinker. Immediate improvement is seen in sleep disorders, mood abnormalities, problems related to poor nutrition and blood pressure, which are enormously influenced by heavy drinking. It also lowers the risk of cirrhosis, cancer, cardiovascular complications, osteoporosis and pancreatitis, with a decrease in costs associated with the physical and mental complications of alcoholism. In addition, subjects who greatly reduce the use of alcohol and those who completely interrupt the assumption, generally show the same benefits in terms of social adaptation.
Reducing alcohol intake without achieving complete abstention is not, therefore, a renouncement to treat the disease. It is possible to consider this type of intervention as an intermediate resource, which can lead over time to complete abstention from alcohol. Many patients who have agreed to reduce their drinking, thinking at first that this was their goal, changed their minds over time to reach complete abstention.
The availability of opioids and anti-reward and anti-dysphoria drugs render harm reduction in alcoholism simple to implement, especially if accompanied by psychosocial support, thereby offering a valid integration with treatments oriented towards complete abstention, according to the following principles:

- many patients prefer to not completely abstain from alcohol, even if they are aware of the risks;
- reduction of alcohol intake represents an additional low-threshold treatment that is non-stigmatising and flexible;
- the results of interventions aimed at alcohol reduction can be as successful as immediate interruption of drinking;
- reduction of alcohol intake is guided by an appropriate strategy in many guidelines for the treatment of alcoholism (EMA, NIAAA, NICE);
- reduction of alcohol intake does not require any particular setting, but does require the collaboration between the general practitioner, specialised services for addiction, alcohology services and psychiatry.

6. Role of neurobiology in the possibility to use a continuum of care

G. Biggio

The development of brain imaging using morphological and functional magnetic resonance, along with images of neurons obtained with super-resolution confocal microscopy, have provided exceptional information on the dynamic and plastic properties of neurons.
Imaging technology, in fact, has demonstrated that neurons are extremely dynamic and plastic cells, with the ability to modify their morphology in real-time and express fairly marked specific membrane protrusions (dendritic spines), in order to enhance or reduce, depending on specific needs, synaptic activity in specific areas of the brain to alter mental functions modulated by those neurons and synapses. At the same time, our understanding of epigenetic mechanisms that control gene function has also provided outstanding information regarding the molecular events through which environmental factors can influence important brain functions. In fact, epigenetic studies have shown that environmental factors can influence gene function and expression of receptors, transporters, various peptides, etc., and has made substantial contributions to knowledge of neuronal function with significant therapeutic implications. These technologies have also been used to study the effects of substance abuse on gene function and morphology and function of neurons, and have opened new horizons of research aimed at better understanding the biological mechanisms involved in the onset of addiction and its treatment.
This research has allowed for the understanding that all abused substances can cause both short- and long-term changes in the function of specific genes that control the activity of selective neuronal populations involved in the modulation of cognitive, emotional and affective function. For example, alcohol, one of the most widely used substances in youth, together with cannabis, has damaging effects on the brain. Even moderate doses can induce functional modifications of specific genes in brain areas such as the nucleus accumbens, amygdala and ventro tegmental area that control pleasant stimuli and gratification, in addition to the prefrontal cortex which has inhibitory control of decision making regarding pleasant or unpleasant impulses. Results at the morphological and functional levels, along with clinical

studies, have allowed us to better understand previously unknown neurobiological mechanisms.
A good example of the importance of these studies, considering damage associated with addictive substances, including alcohol, is the discovery that: a) in both sexes the brain becomes adult when the prefrontal cortex, the area that processes decision to try (or not) a certain substance, reaches its maximum thinness (23-25 years in females and 26-28 years in males), while b) the nucleus accumbens, which controls gratification, motivation and pleasure in the adolescent has a volume approximately twice that seen in adult subjects. This anatomical data is of crucial importance for understanding why adolescents are more vulnerable than adults to become addicted and consume excessive amounts of alcohol. In fact, the lack of effective inhibitory control by the prefrontal cortex at the time when the pleasure nucleus is still overdeveloped constitutes an element of elevated vulnerability for the adolescent towards psychopathology.
The excessive consumption of alcohol in the range of 10-28 years can thus represent an elevated risk for neuronal toxicity. In fact, even at moderate doses alcohol inhibits neurogenesis (proliferation, development and survival of neurons), which is extremely active in the brains of children and adolescents, thus reducing neuronal plasticity and inhibiting the formation of dendritic spines and synapses. The effects, mediated by the epigenetic processes of methylation and acetylation activated by ethanol at specific genes, can justify the greater vulnerability of adolescents to become chronic drinkers. The evidence that alcohol, like all addictive substances, induces changes in gene function that are difficult to revert, suggests that it is crucial to have pharmacological and non-pharmacological approaches to favour early prevention and reduce the intake of alcohol.
The above-described neurobiological data suggest the critical importance of activating, at both the social and medical levels, early prevention mechanisms especially towards younger individuals through effective information programmes and training, in addition to adults who abuse alcohol. The evidence that alcohol has a high level of toxicity at both the genetic and neuronal levels should prompt creation of programmes focusing on reduction of alcohol consumption, even in subjects who are not alcoholics, since it is potentially toxic even at moderate doses. The evidence that neurons, through modulation of gene function, are extremely sensitive to the action of both drugs and environmental factors highlights the importance of using pharmacological therapies in combination with effective psychosocial support programmes to ensure an optimal continuum of care in the treatment of alcoholism.

7. Role of impulsivity and the psychiatric approach in the continuum of care of the patient with alcohol use disorder and a dual diagnosis

C. Mencacci

The therapeutic approach to alcohol dependence is complex and varied, and is characterised by a range of clinical sensitivities that should give rise to a specific and individualised approach in each patient. The complexity of intervention reflects the multifactorial nature of alcohol dependence. The use of alcohol typically begins in early adolescence, and the amount of alcohol consumed tends to increase around 20 years of age, decreasing in adulthood with the acquisition of a social and working role [20]. Such a longitudinal scheme is not followed in alcohol-dependent subjects. In the attempt to describe the evolutionary trajectories in the use of alcohol, with the aim of defining a taxonomy of dependent behaviours, several groups of subjects have been defined based on alcohol consumption. In particular, four subgroups have been identified: i) antisocial alcoholism; ii) developmentally cumulative alcoholism; iii) developmentally limited alcoholism (limited over time); iv) negative affect alcoholism (secondary to modulation of negative emotions) [21]. In contrast, four trajectories have been correlated with alcohol use: i) no tendency to abuse; ii) patients with infrequent abuse; iii) patients with early onset; iv) patients with late onset [22]. Globally, in identifying the causes and possible outcomes of the use of alcohol at a young age, in general the age of onset and frequency/intensity of use are both associated with poor prognosis. Focus has also been placed, however, on the analysis of which variables correlate with the various trajectories of abuse, and to identify variables that can predict such behaviour. Among the variables at a young age associated with alcohol dependence, in an adult age, the following have been noted: male gender, family history of dependency, temperamental behaviour of high impulsivity (high novelty seeking, low harm avoidance), behavioural alterations and presence of psychiatric symptomology (anxiety spectrum disorders or predominately affective).
Alongside these individual variables, the role of peers should be highlighted (which tends to increase all impulsive behaviours). These data suggest that a patient predisposed to alcohol dependence is a patient with a particular individual constellation of factors and who presents some form of distress/mental suffering. In this regard, data on comorbidities are interesting: almost 30% of patients with a psychiatric diagnosis have a positive history for alcohol abuse/dependence [23]. Comorbidity is found not only between psychiatric disorders and alcohol dependence, but a cluster of dependencies has been found,

including both physical and behavioural dependence, which suggests a common predisposition to addictive behaviours, in turn associated with a particular biological-temperamental constellation [24]. Significant overlap has recently been found between alcohol dependence and the major psychiatric disorders, providing the basis for the concept of comorbidity and dual diagnosis: in this light, the use of alcohol falls within the broader context of the modulation of mental state of an individual [25].

An important theme, which can provide a theoretical basis for the high levels of comorbidity between various forms of addiction and psychiatric symptomology, appears to be related to the potential effects of risk of these conditions due to early exposure to traumatic factors: much attention has focused on the role of physical and sexual abuse in the development of alcohol dependence [26]. Expanding the horizon, more recently, researchers have begun to consider how exposure to factors (even non-traumatic) is capable of causing epigenetic alterations, and how such factors are linked to late development of alcohol dependence. In this case, the question of alcohol addiction is part of a larger broader consideration related to early development factors associated with cerebral changes that predispose to subsequent psychiatric symptoms or alterations in behaviour [27]. The interaction between genetic susceptibility and environmental factors may influence an imbalance in the genetic control of corticotropin-releasing factor, the hyperactivation of which favours development of alcohol dependence [28].

All of the above considerations support clinical experience and reinforce the knowledge that alcohol abuse or dependence tends to manifest as a behavioural response to a psychic signal/malaise, adding to other forms of abnormal behaviour that are often associated with dependence (self-harm, other forms of addiction). Even the relational link between alcohol abuse and impulsivity, which has been identified as one of the endo-phenotypes correlated with late development of dependence, is very important from a clinical viewpoint and reveals how alcohol can be used as a tool to overcome situations that are deemed difficult to overcome with coping skills alone: alcohol, in fact, can act as a "social lubricant" that helps the individual to overcome inhibitions or social phobias, reduce anxiety and favour affective dissociation (e.g. renders sexual relations easier without affective impairment). Likewise, the presence of anxiety symptoms or depression is often a decisive factor in the use of alcohol as an easy solution to complex situations: in fact, alcohol has an anxiolytic effect (which aims to lessen the sense of inability, self-esteem deficits, difficulties in achieving a standard level), anaesthetic/pain relief effects (e.g. used during mourning or to tolerate frustrations and failures) and antidepressant and euphoric effects.

Careful psychiatric screening of subjects with alcohol abuse or dependence (especially in minors and young adults) would allow for recognition of psychic pathologies that often remain silent, hinder treatment and prognosis, and lead to a self-maintaining vicious cycle. Alcohol abuse, as a visible sign, is also a signal that should lead adults to question their role as an adult and as a guardian of the young, in fact exposing a background of mental suffering.

8. New concepts of acceptance and care of patients with alcohol use disorders in addiction services

C. Leonardi

Local/territorial services for addiction (SD) are healthcare structures that are involved in dealing with any problem concerning the use, abuse and dependence on illegal and legal psychotropic substances. SD have recently extended therapeutic interventions to addictive behaviours that do not involve substance abuse. In summary, their job is to provide interventions for prevention, diagnosis, care, health promotion and rehabilitation of people with disorders related to addictive diseases. A team of addiction experts works within an SD: doctors, psychologists, sociologists, social workers, educators, nurses and healthcare assistants, who can provide knowledgeable answers that are tailored to the different needs of individual patients and their families. Among the specific duties of the SD, it takes part in diagnostic 'treatment' of the patient in order to identify the most appropriate multidimensional therapeutic strategies, which can also be provided by accredited public and private local services. In general, treatment of alcohol use disorder can be carried out within the structures of the SD, which are often organised in specific units for alcohology. In SD within larger departments, the Alcohology Unit can be located in a different structure.

Continuity of therapy and territorial networking are essential elements in treatment of alcohol use disorder and individualised treatment. Therapy should include diagnostic-therapeutic support by the SD together with hospitals, mental heath departments, general practitioners, pharmacies, social services, regulatory and legal systems, mutual aid groups and community rehabilitation.

Given these premises, it is clear that the endpoint of any alcohol-related therapeutic project should be directed by personalisation of treatment and, above all, as a natural evolution of individualised therapeutic strategies. It should not be obsessively characterised by achieving an immediate alcohol-free state, which considering the psychopathological profile of the alcoholic will certainly result in treatment failure in some individuals. While achieving a state of abstinence is relatively easy for mo-

tivated patients, for others it is a goal that is difficult to reach and should be gradually introduced through a preliminary process of stabilisation of symptoms and craving of alcohol. As a consequence, immediate improvement of the patient's overall conditions and quality of life can be attained.
This new mode of interpreting the treatment plan for an alcoholic is different from an ideological and stereotyped approach to cure drug addiction and is oriented towards defining a continuum of care that involves all members of the therapeutic network in the process of individualisation of therapy for alcohol use disorders. The treatment plan needs to take into account the therapeutic needs of the patient, his family, social situation and, above all, the different historical phases of the addiction and relationship with the substance.
At present, therefore, overcoming alcohol addiction should be built upon new capabilities and therapeutic opportunities that must not harm the real and tangible needs of the patient. It should promote the process of voluntary change through pharmacological interventions aimed at social control, "step-by-step" improvement in health, reduce risks related to alcohol and the achievement of a state of sobriety through reduction in consumption. This new bio-psycho-social approach, in which the concept of reduction vs. abstinence is intensely strategic within any course of treatment for alcohol use disorders, can provide new opportunities for personalised care, and should be adopted by all those involved in the treatment network, including the SD.
Such an approach can be considered decisive both from mental and biological points of view. At the mental level, it is useful in all patients whose motivational phase is still in that of "pre-contemplation". This allows them, in the short-term, to stabilise the compulsive use of alcohol within acceptable parameters without having to accept a therapeutic target based solely on achieving a state of abstinence and to create a motivational substrate for a more lasting and stable subsequent course of treatment. At the biological level, it strategically addresses the frequent condition called "cognitive anosoagnosia", or the dramatic functional limitation of the prefrontal cortex that is responsible for the lack of awareness of the condition in the compulsive alcoholic which leads the individual to unknowingly disavow or minimise the problem and severely limits compliance to therapy in the early stages.
It would thus appears evident that together with multidisciplinary therapies of the SD, pharmacotherapies based on deactivation of receptors sensitive to the action and control of alcohol and alcohol-related dysphoria can offer a valuable tool to help the alcoholic within a therapeutic alliance to minimise the effects of the "first glass" and favour a gradual reduction of compulsive drinking. Modulators of the opioid system with distinct antagonistic effects on μ and δ receptors, associated with the partial agonism on κ receptors, in addition to allowing individualisation of treatment on the above-mentioned assumptions, are particularly appropriate because, thanks to their pharmacodynamic properties, do not pose any risk of an additional neuro-psychotropic effect between alcohol and drug itself.

9. The role of residential programmes in the continuum of care

M. Cibin

Interventions in alcohol use disorders are generally provided in three types of structures: i) out-patient settings; ii) residential facilities; iii) mutual help groups (AA, CAT). It has long been held that these interventions should be seen as separate and not overlapping: the present vision, however, is that of a continuum of care, or the synergy of different approaches in building a coherent course of accessible and effective treatment. In Italy, residential treatment for alcohol use disorder is available as: i) hospital admission for detoxification; ii) rehabilitative hospital-sponsored programmes; iii) community therapy programmes. The uniqueness of community therapy compared with other types of programmes lies in their greater personalisation of intervention in terms of duration and objectives, in addition to a focus on a sense of belonging and personal responsibility, which is especially valued as part of an equal relationship that characterises community life [29].
Persons with alcohol use disorder can be classically divided into two groups: i) Cloniger type 1 [30] in whom the dependence arose in an adult age and is correlated with life events; ii) Cloniger type 2 in whom the dependence arose in adolescence, has a genetic basis, and is associated with impulsive traits and antisocial/borderline personality disorder. In both cases, in the pathogenesis of addiction, traumatic events play a role: in type 1, they occur in the form of isolated trauma in adulthood, while in type 2 they are linked to repeated childhood events that affect a genetically predisposed individual.
With regards to residential programmes, in type 1, a short program is indicated that contains, in addition to the parts most closely related to addiction (motivation, relapse prevention, facilitating self-help), post-traumatic psychotherapy (exposure therapy, emotional release, mind-body interventions) [31]. In the treatment of type 2, however, the focus is on association between personality disorder and substance use: programmes that combine these interventions for dependencies with specific interventions for personality disorders are therefore indicated.
In light of these considerations, the ideal residential pro-

gramme for alcoholism should include an initial diagnostic/motivational part, on the basis of which patients can be assigned to a "post-traumatic" treatment (type 1) or treatment for dependencies/personality disorders (type 2); these therapeutic phases can be followed, if necessary, by a rehabilitative phase focusing on the acquisition of social and working skills. Currently, in Italy, only 'fragments' of the ideal programme can be found in selected residential centres [32], while to our knowledge there is no programme that meets all of the above criteria.

According to the Ministry of Health, 6.8% of clients have received residential or semi-residential treatment (2.7% in community, 2.9% in hospital, 1.2% in accredited private structures): residential treatment, in general, and therapeutic communities, in particular, still offer marginal treatment considering the complexity of interventions for alcohol use disorders.

The factors that limit the use of these resources are: i) cost; ii) appropriateness of therapy; iii) relationship with the network; iv) relationship with the patient. Regarding the latter, the capacity of residential programs to participate in the continuum of care is closely related to individualisation based on the characteristics of patients and their motivation. Relational methods are critical to the effectiveness of intervention and reduction of drop-outs: it is no coincidence that interventions aimed at facilitating motivation to change are considered an integral part of intervention for alcohol use disorders. Building a relationship, encouraging change and supporting self-help are essential elements of a motivational approach, and have the goal of defining objectives with the patient and the course of treatment. At present, almost all residential programs are aimed towards abstention. However, using 'motivational logic', it is possible to hypothesise that customised and gradual goals can be defined in which they play a key role in strategies aimed at reduction. The objective is for the patient to have an increasingly active role in the therapeutic process, and not individuals marked by dependence, but citizens who have experienced addiction as an "accident", who maintain their freedom of choice and the ability to assume the responsibilities of life.

10. The point of view of the general practitioner with a focus on addiction

A. Rossi

Alcohol is one of the key determinants of human health. The strategies that national healthcare services put in place against alcohol-related problems inevitably crossover with one another. With a specific focus on the general practitioner, it may be most straightforward to pose a few simple questions.

- Is it useful and necessary to extend current types of health intervention to alcohol?
- Should intervention be extended to primary care settings?
- What types of intervention should be considered within a primary care setting?
- Is the general practitioner adequately trained to intervene in alcohol addiction?
- What obstacles and difficulties should be taken into consideration?

Is it useful and necessary to extend current types of health intervention to alcohol?

In Italy, in 2012, according to the available data there are approximately 700,000 subjects over the age of 11 years who can be considered 'at-risk' or affected with alcohol-related problems or pathologies, according to the definition of the WHO. In the same year, only about 69,000 subjects were in treatment at Alcohology Centres. These numbers alone should provide an adequate answer to the question.

Should intervention be extended to primary care settings?

The general practitioner has the role of evaluating the patient's lifestyle and approaches correlated with alcohol-related problems or disease, in whatever means they are presented. As for screening and evaluation of interventions for problems related to the use of alcohol (as for tobacco and drugs), any type of intervention is realistically feasible provided that there are clear objectives and limits. While in the setting of general medicine alcohol-related problems present in a heterogeneous manner, the situation is different in specialised centres where patients present at an advanced stage of dependence and/or confirmed polyabuse. Even in these circumstances, the general practitioner must play a key role. On the other hand, at a European level the importance of prevention and early detection by the general practitioner is stressed, at least for target individuals defined as "problem drinkers", i.e. those not yet affected by addiction and who are prone to reduce their drinking when recommended by their physician.

What types of intervention should be considered within a primary care setting?

Unquestionably two: early detection and brief intervention. In some cases, pharmacological intervention can be provided. Concerning early detection, it is our belief that a periodic structured interview is not possible for all patients. It is thus preferable to consider specific situations, previously recognised through individual case findings or in groups of individuals at particular risk. The general practitioner must therefore resort to scrupulous recording of medical history of alcohol consumption and of any events, symptoms, or signs that would be useful to identify subjects to be assessed more carefully. In this regard, the administration of tests may be

useful, such as the shortened version of the AUDIT-C, which according to the WHO is the most reliable test in primary care settings. It should, however, be noted that an informal and open interview seems to provide sensitivity, specificity and predictive values that substantially overlap structured questionnaires [33].

In subjects in whom a problem has emerged, and in those with a positive AUDIT score, brief intervention is desirable. Such intervention has shown to be significantly effective by many studies (and particularly in the setting of general medicine) in terms of reduction of alcohol consumption. Brief intervention is sustainable in terms of time and is workable in terms of educational and communicative adequacy of the general practitioner. Lastly, new methods of treatment compared to pharmacological therapy of alcoholism and the availability of easy to manage drugs, allow the general practitioner to outline interventions that are not limited to detection and management of alcohol-related diseases, but that, in selected cases, involve medical therapy.

Is the general practitioner adequately trained to intervene in alcohol addiction?

The answer to this question is potentially complex and protracted. For the sake of brevity, we can state the general training at medical school, the many constraints in current practice, organisational barriers and the lack of defined pathways for clinical care, make the general practitioner, in many cases, to underestimate this type of problem among his/her patients.

What obstacles and difficulties should be taken into consideration?

The answer to this question overlaps somewhat with the previous. The summary of the explanations given below was taken from a survey carried out by the Italian Society of General Practitioners on prior training activities. The motivations provided in this light were: i) lack of time; ii) fear of conflicts with the patient or to promote conflicts within the family or the couple; iii) perception of limited or lack of effectiveness of treatment; iv) the belief that patients with this type of problem do not show or have only poor response to treatment; v) inadequate knowledge of counselling techniques and brief intervention.

In conclusion, a simple but effective "package" of therapeutic tools, used in the setting of general medicine in collaboration with the specialist, could include: i) motivational counselling and relapse prevention; ii) pharmacotherapy, iii) referral to specialised services and self-help groups. The availability of safe and easily manageable drugs can undoubtedly favour involvement of general practitioners in diagnosis and treatment of alcohol-related problems.

11. Alcoholism and the network of territorial services

P.P. Pani

There are some areas that, given the complexity of the healthcare and social factors involved, are more amenable to an integrated approach in which the specialisation and fragmentation of interventions can result in damage, especially where specialists tend to focus on their obligations rather than pass on information [34]. Alcohol dependence is a classic example, since it is a condition for which the association of psychosocial interventions with pharmacological therapy, continuity of care, case management and integration and coordination of interventions leads to different levels of care and services, offering undisputed benefits [35 36]. However, there still remains the problem of integration between professionals, services and institutions. In the national context, the case of alcoholism is emblematic, where the sectorial approach affects the integration of interventions for alcohol dependence and those for dependence on other substances even when they involve the same individual. In the National Health Service, optimal integration for interventions aimed at treatment of addiction should be ensured by an orthogonal matrix system where each unit is placed in the same district (ensuring the integration of services and institutions) and in the Department (ensuring the scientific-technical quality of interventions). In this type of organisational model, services for addiction may follow a "hub and spoke" pattern, which concentrates the general functions of operational planning, coordination and clinical services in a hub. The other "nodes" and "points" are "the spokes", whose activity is highly integrated with the hubs, are distributed throughout the territory, and are represented by structures and operational realities that can more easily fulfil requests for assistance (territorial operating units: territorial units for alcoholism, smoking, etc.; general practitioner ambulatories; mental health centres, family planning clinics, social services, etc.). Such a scheme has the aim of ensuring a uniform system and makes timely use of technical and professional skills and resources anywhere within the network, limiting transfers of clients to specific situations and time phases on the basis of the overall therapeutic and rehabilitative course. The realisation of this type of system could initially start with a pilot project, similar to those implemented abroad [37], with the participation of services for addiction and other relevant healthcare and social structures.

Further interventions could be aimed at encouraging good behaviour in the achievement of defined levels of integration. In fact, current systems of payment for services do not take into account the value of integra-

tion and coordination and do not provide incentives to encourage dialogue between the different levels of care. The inclusion of continuity of care in basic levels of care could also be considered to add further economic value. The establishment of an appropriate level of assistance to ensure integration and continuity of care implies, however, the adoption of legislative and regulatory choices that resolve critical issues relating to general forms of horizontal (between institutions, services and healthcare and social operators) and vertical (between key structures, services and operators who define the functions of basic, specialist and hospital care) integration of the different areas of expertise, organisation, performance and forms of financing.

12. The continuum of care and economic prospects of new paradigms for therapeutic management of the alcohol dependent patient

G. Turchetti

In addition to representing a serious public health problem, alcoholism is a major expense in terms of both healthcare and social resources. In Europe, it is estimated that the social expenses related to alcohol are about € 155.8 billion, while in Italy the social costs are estimated at € 22 billion [38]. Undoubtedly, the magnitude of social costs, which incorporates the direct costs of healthcare, direct and indirect non-medical costs and intangible costs associated with alcoholism, must be considered when contemplating strategies that adequately address the phenomenon of alcoholism and its associated implications.

The knowledge of the importance of the overall health and economic burden caused by alcoholism is in fact the first step towards better management of the problem. Bottom-up strategies with sufficient long-term investments are needed for better preventive measures and profound cultural change. On one hand, this would help to reduce the number of individuals who become alcoholics, and on the other to help those who approach the treatment centres for alcohol addiction in a society that has certainly overcome stigmatisation of alcohol dependence. These strategies will allow increasingly better results from an economic point of view.

However, the strategies that can provide significant results in the short to medium term should be achieved through optimisation of the diagnostic-therapeutic course of the alcohol dependent patient. In fact, by changing the continuum of care towards better systematic coordination and organisation of all those involved to maximise skills and intervention strategies, health indicators can be improved and the economic burden on society due to alcoholism can be reduced.

What is, therefore, the best model for treatment of alcohol dependence? Without question, this is the model that allows for achieving abstention, or the 'absolute best', from health, economic and social viewpoints. However, in both medicine and economics, pursuit of the absolute best is characterised by a more or less long sequence of relative bests, i.e. to achieve the best possible results within the given conditions. Thus, the question 'What is the best model for treatment of alcohol dependence?' becomes 'What is the best model to cure the individual patient in the specific phase of his disease, considering the specific clinical personal, family, and environmental conditions?' What is the realistic target given these particular constraints? In this way, the search for the absolute best is transformed into the search for the relative best. From achieving abstention, for example, to achieving a reduction of harm. By reaching that target and stabilising the situation, the patient enters another phase of management and another target can be set, another relative best. From an economic standpoint, therefore, the search for reducing the possibility of accumulation of harm is not a renunciation (abdication, an admission of impotence) in achieving a 'first best' objective – abstention and the total recovery of the patient – but the pursuit of an intermediate target, a relative best, on the way towards the absolute best. It must, however, be kept in mind that for some patients the relative best may be the only result to strive for in the medium to long term. While this may not be completely satisfying, from an economic point of view it is certainly preferable to reduce harm and reach an "acceptable" target rather than to fail completely in the pursuit of a more desirable 'first best' that cannot be achieved.

What is the economic impact, and social cost, of a therapeutic strategy of the alcoholic patient whose target is reduction of harm? If from a clinical point of view the availability of instruments that allow differentiation of therapeutic strategy depending on the stage of the disease and family and social conditions is undoubtedly desirable, this would permit a greater variety of targets and therapeutic strategies, even from an economic point of view, to reduce the burden of disease on society. In fact, by definition, an intermediate sub-optimal target, a relative best, is more likely to be successful compared to the ultimate optimal goal of absolute reduction of alcohol-related harm. Thus, in patients who reach this target significant savings in terms of health and social costs can be achieved. Reduction of harm is thus a desirable target, even from an economic point of view.

Greater individualisation of the target and of the relative therapeutic approaches that, in a continuum of care, brings to a series of intermediate targets, a dynamic sequence of relative bests from a clinical point of view, is the strategy which reduces further the weight of alcoholism on society even from an economic point of view.

13. Towards the future … the continuum of care even in alcohol use disorders

I. Maremmani

The interest in reducing at-risk drinking, made possible by new therapeutic possibilities, may, in the near future, allow for a new therapeutic organisation for alcohol use disorder. As for other medical specialities, assistance will be organised by level of intervention. In fact, there is no scientific evidence of better results in the case of non-adoption of the general principles of treatment of chronic diseases (criterion J). Patients with alcohol use disorder should be treated as normally as possible, without resorting to the established schemes that tend to be based on rigid and stigmatising rules (criterion K).

Level 1 (the first level of intervention) is represented by the general practitioner; level 2 (the second level of intervention) includes specialised services dedicated to alcoholism, drug abuse and dual diagnoses, in addition to problem drinking in psychiatric patients (in this way it is possible to intervene in a selective manner on the different phases of alcohol use disorder, from onset to psycho-physical decompensation and even the second level of severity). A patient could, therefore, be treated at the ambulatory clinic of his general practitioner or psychiatrist's office, not outside the National Health Service, and return to their observation after specialist intervention for increasing severity. Level 3 (third level of intervention) is represented by services at University clinics that are specifically dedicated to non-responders or particularly complex cases. The general practitioner will work as an intermediary between the general population and specialised centres. Specialised services will operate as outpatient facilities and as shelter facilities through agreements with therapeutic communities (first level of admission) and, in person, at hospitals (second level of admission). The University will operate in third level assistance with specific outpatient services and hospitalisation for treatment-resistant patients; knowledge will be transmitted through teaching (medical degree, nursing, psychological and sociological disciplines), specialisation, research and post-graduate teaching (level 1 and level 2 masters, CME in medicine) (Fig. 2). This model, widely used for all chronic disease, is defined as 'shared care' or a 'mixed care model'. Only this model can adequately treat alcohol use disorder by minimising negative interference due to rigidity of treatments and stigma that are currently applied.

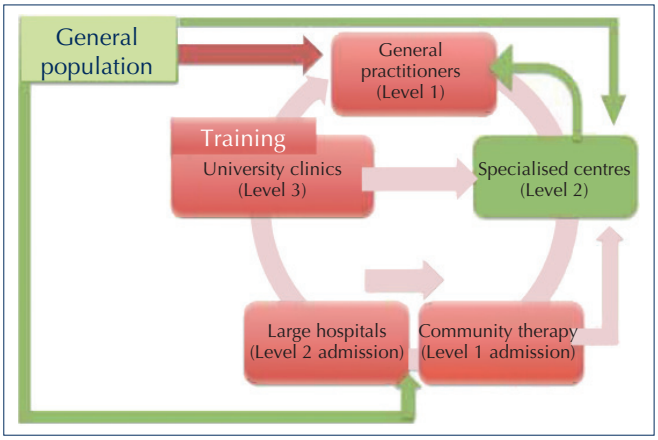

FIGURE 2.
Future prospective for treating patients with alcohol use disorder in Italy. *Prospettive future dell'assistenza ai pazienti con disturbo da uso di alcol in Italia.*

In an integrated vision of the disorder, work is needed on a cultural level to reinforce the complementary nature of psychosocial and pharmacological interventions that are not specifically dedicated to promote or maintain a state of immediate abstinence from alcohol. In addition, this is especially true in order to offset the marginalisation, more or less hidden, to which patients with alcohol use disorder, who "do not want" or "cannot at the moment" stop drinking completely, are often subjected. Integration, without any doubt, will be the cornerstone of this activity and will form the core of a new philosophy of integration between therapeutic approaches. Patients must be integrated in a civil society, within which they have become dependent and in which, in order to call them cured, must be cured, thereby creating a genuine and concrete path of recovery, from reduction of drinking at risk to complete abstention.

Pharmacological intervention in itself, even if extremely innovative, is not able to bring about a new philosophy of treatment of addictions. Those who cure depression know which drugs bring about a faster return of the patient to employment, limit impact of the care pathway on social life and allow patients to be cured within their social context. For alcoholism, such reasoning has struggled to emerge when the drug in question allows "only" a decrease in at-risk behaviour.

At the present state of neuroscientific knowledge, it is possible to go one step further in the logic that led to the integration of psychosocial and pharmacological approaches, to remove the shadows of social judgment and to aim for a course of treatment towards absolute abstention. In fact, when abstention is not considered the ideal therapeutic target for a given patient because he/she is unwilling to accept it, which therefore represents a de facto barrier to treatment, new therapeutic modalities should be identified and integrated approaches that motivate patients towards a path of individualised treatment should be considered.

This allows for care of individuals who would never enter into a rigid path of care, even when they are on the verge of losing their role as father, worker, or who are mem-

bers of families with high social standing. Accompanying these patients through reduction of alcohol intake to complete abstention will be a historical evolution, which can only be achieved by investing in a network of comprehensive services that are integrated within healthcare and social structures.

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Multi-modality as a new pharmacological approach for treatment of depression: the role of vortioxetine

La multimodalità come nuovo approccio nel trattamento della depressione: il ruolo di vortioxetina

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Summary

Recent evidence, such as that from the STAR-D study, have demonstrated that several unmet needs are still present in the treatment of major depression. The "classical" approach adopted to develop new antidepressants drugs, based on selectivity, did not result in increased remission rates in clinical practice, whereas multi-modality represents a new approach to develop novel antidepressants endowed with multiple actions that affect several pharmacological targets. Multimodal antidepressants, developed in the last three years, act through at least two pharmacological modes of action (serotonin reuptake inhibition, agonist/antagonists on neurotransmitter receptors) on at least two or more pharmacologic targets. Vortioxetine is a novel multimodal antidepressant that exerts its antidepressant efficacy in animal models of depression through a combination of two pharmacological modes of action: reuptake inhibition and receptor activity. In vitro studies indicate that vortioxetine is antagonist of 5-HT$_3$, 5-HT$_7$ and 5-HT$_{1D}$ receptors, a partial agonist of 5-HT$_{1B}$ receptors, an agonist of 5-HT$_{1A}$ receptors, and inhibitor of the serotonin transporter. The combination of 5-HT$_{1A}$ agonism with 5-HT$_3$ antagonism can explain the rapid 5-HT cell firing induced by vortioxetine compared to SSRIs such as fluoxetine. Vortioxetine is also able to activate the glutamatergic system in the rat frontal cortex through antagonism at 5-HT$_3$, 5-HT$_7$ receptors. All these pharmacological modes of action can contribute to explain the increased clinical efficacy of vortioxetine in the treatment of cognitive symptoms of depression. Cognitive deficits in depression are often associated with both a suboptimal response to antidepressants and reduced remission rates. Vortioxetine is the first multimodal antidepressant available for the treatment of depression with a specific, positive impact on cognitive symptoms.

Key words

Depression • Serotonin • Multi-modality • Glutamatergic System • Cognitive symptoms • Vortioxetine

Introduction

Depression is one of the most common and invalidating psychiatric disturbances with an incidence of 17-18% in the general population [1 2]. In general, depressive disorders are characterised by significant burden and have enormous impact on patients. They are thus costly not only in terms of healthcare expenses for pharmacological therapy and hospitalizations, but also from social, occupational and personal standpoints. It Italy, at least 1.5 million individuals suffer from depression, while 10% of the population, or about 6 million individuals, have experienced at least one episode of depression during their lifetime [3]. According to the projections of the World Health Organization (WHO), by 2020 depression will be the second leading cause of disability worldwide after cardiovascular disease. Depressive symptoms are frequent in the elderly (> 65 years), and the number of elderly individuals suffering from depression will undoubtedly increase due to the progressive ageing of the general population. Considering gender, women, especially those with an age between 40 and 50 years, are twice as likely to be affected by depression compared to men [4].

Unmet needs in the pharmacological treatment of major depressive disorder

Depression can be diagnosed and treated with pharmacological therapy, despite data from the WHO indicating that less than 25% of affected individuals have access to effective treatments. In the last 60 years, a number of antidepressants belonging to various classes have been developed, which have allowed for improvements in therapy and prognosis of major depressive disorder (MDD). Nonetheless, there are still a number of unmet needs including: slow onset of action, sub-optimal effi-

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cacy, presence of residual symptoms, inefficacy on comorbid cognitive symptoms, treatment of comorbidities, management of elderly patients with depression and problems related to tolerability.

Even if selective serotonin re-uptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are generally considered as first-line therapy in the treatment of MDD, according to the guidelines of the National Institute for Health and Care Excellence (NICE), about 20–30% of patients with depression do not respond to first-line therapy [7]. Many studies have demonstrated that 60-70% of patients respond to initial antidepressant monotherapy [9], and that more than one-third of patients treated for depression become resistant to therapy even when initial treatment was correctly chosen, administered for an adequate length of time and properly dosed [6]. The correlation between an inadequate response to initial treatment and worsening of prognosis necessitates, therefore, the identification of new agents that provide better clinical response to initial therapy.

Remission, considered as the primary objective of therapy, is defined as a reduction or absence of symptoms for a prolonged period of time [10]. The most common definitions to identify remission in clinical studies are: MADRS ≤ 10, HAM-D17 total score ≤ 7, or CGI-S ≤ 2. Unfortunately, a significant proportion of patients (around 32%) who meet criteria for remission continue to show residual symptoms that are generally more subjective than objective, but which nonetheless have a negative impact on long-term outcomes [8-10]. The presence of residual symptoms is associated with early recurrence and with a reduction in the quality of life and a greater risk of suicide. In the STAR-D study, patients who responded to therapy and who did not experience remission reported 6-7 residual depressive symptoms. The most common included insomnia (94.6%), sadness (70.8%) and decreased concentration (69.6%) [11].

Current treatments help to resolve depressive symptoms in many patients, but in others leave a number of residual symptoms, especially cognitive symptoms [12]. In fact, cognitive symptoms have recently been considered as a critical factor in persistence of disease and in occupational and social disabilities during MDD [13-15]. The association between cognitive deficits, limitations in functioning and major depressive episodes was highlighted in a survey of over 21,000 individuals within the European ESEMeD study [15]. In that study, it was reported a strong association between major depression and cognitive dysfunction, and in particular deficits in concentration and attention. Current antidepressants help to improve mood in many patients, but have limited clinical efficacy in the treatment of cognitive symptoms [12 13 16].

Even if cognitive dysfunction is often unrecognised by the physician, it is nonetheless worrisome for many patients. In a prospective clinical study, more than for other symptoms, patients complained of the presence of at least one cognitive symptom for 94% of the symptomatic period, for 44% of the time during remission and for 66% of the time during three-year follow-up [12].

In patients with MDD who respond to therapy with an SSRI or SNRI, but who are not in remission, cognitive dysfunction persisted in 70% of cases with a reduction in concentration and/or decision-making [25]. In addition, it is known that tricyclic antidepressants (TCA) have a negative effect on cognitive function due to their anticholinergic properties [16]. Taken together, these data show that there is still the need to improve cognitive functioning in patients undergoing treatment with antidepressants.

Another important aspect to consider is that many patients cannot tolerate antidepressant therapy due to adverse effects. In fact, around 50% of patients discontinue antidepressant therapy within 6 months of treatment [17]. Even if adverse events such as nausea and diarrhoea can lead to early discontinuation of treatment, these effects are usually of short duration and resolve after 2-3 weeks. However, long-term adverse effects such as sexual dysfunction, insomnia and weight gain may be present throughout the entire treatment period, and thus have a significant impact on the quality of life and compliance [18]. For persistent or severe adverse effects, guidelines recommend dose reduction, switching to an antidepressant with less propensity for the side effect in question, non-pharmacological treatment, or symptomatic treatment [19]. Nonetheless, the potential benefits of using additional drugs to treat side effects should be evaluated in light of the added risk in terms of safety and tolerability [20]. This approach, however, will considerably increase the costs of therapy.

Treatment-emergent sexual dysfunction (TESD) caused by antidepressants is a problem of considerable importance that can lead to early discontinuation of therapy. The incidence of TESD can be as high as 70% depending on the type and duration of antidepressant therapy [22]. SSRIs are associated with a relatively high propensity to cause sexual dysfunction, and for this reason should be used with caution in patients with pre-existing symptoms related to sexual dysfunction as they could be aggravated by pharmacological treatment [5].

In some cases SSRIs can cause sleep disturbance in patients with depression [23]. Diverse effects have been observed with different types of SSRIs: while fluoxetine and paroxetine are known to delay the REM phase and reduce the duration and efficiency of sleep, sertraline is associated with an increase in the duration and efficiency of sleep and reduced night-time awakenings [23]. Among the SNRIs, venlafaxine increases the time of REM sleep, but can reduce the total duration of sleep [21]. It has been demonstrated that sleep-related adverse

events are the most common cause of discontinuation of treatment with SNRIs in adults [23]. Early relief of insomnia in patients with depression, however, can increase both compliance to treatment and overall functioning, while complete resolution of insomnia significantly improves prognosis in MDD [9].

Weight gain is another common adverse effect that is rare with acute treatment, while it is more frequent during long-term antidepressant therapy. Weight gain is a significant problem in terms of tolerability and is associated with low acceptance to therapy, and consequently with a reduction in long-term compliance [24]. The incidence of weight gain is 18–50% in patients undergoing antidepressant therapy in open-label clinical studies [18]. One of the unmet needs in clinical practice is thus the need to develop new antidepressants that have a better tolerability profile compared to SSRIs and SNRIs, with a lower incidence of side effects including sexual dysfunction and weight gain [37].

New pharmacological targets in treatment of major depression: a new class of multimodal antidepressants

Treatment of MDD during the last 50 years has been mainly based on the monoaminergic hypothesis. However, several lines of evidence have suggested that the monoamine theory of depression is too simplistic to explain a syndrome as complex as depression and the lack of clinical remission in up to 60-70% of patients. The limitations of the monoaminergic hypothesis have emerged from preclinical and clinical studies [26]. Preclinical studies demonstrated that delay between the rapid modification at the synaptic level of biogenic amines in the acute phase and the therapeutic effects seen after at least 3-4 weeks cannot be explained only by the decreased expression of tyrosine hydroxylase and β-adrenergic and serotoninergic (5-HT_{1A}) receptors; it is believed that progressive alterations of specific signalling pathways (CREB, GSK-3beta, AKT/mTOR) related to activation of neurotrophic factors (e.g. brain-derived neurotrophic factor, BDNF) leads to a subsequent impairment [27-29]. These studies suggest that independently of the main 'monoaminergic' activity of many currently used antidepressants, in order to be clinically effective these drugs likely interfere with various signalling pathways that are downstream of monoaminergic receptors. These include BDNF, mTOR and AKT/GSK 3beta signaling pathways, that have driven recent interest in the development of new antidepressants with higher rates of clinical remission [29 30].

Recent evidence, starting with the STAR-D study, has demonstrated that there are still many unmet needs in pharmacological treatment of MDD. An approach based on 'selectivity' focused on a single pharmacological target (e.g. serotonin transporter, SERT) has not led to high rates of remission in controlled or observational studies. Actually, different studies are focused on residual symptoms, which unfortunately prevent the achievement of remission in clinical practice. In this regard, increased attention has also been placed on cognitive symptoms as they are frequently present in many forms of depression that show a sub-optimal response to SSRIs and SNRIs.

Such new evidence implicates that compared to a classic approach adopted to date with selectivity of intervention on individual monoaminergic systems, new multimodal approaches are centred on the development of agents having antidepressant activity with multiple mechanisms of action and that interact with multiple pharmacological targets. According to this scenario multimodal antidepressants can modulate neurotransmitter systems, such as the glutamatergic, dopaminergic and cholinergic, that have not been adequately considered in the treatment of major depression [30 38] (Table I). Multimodal drugs with antidepressant activity developed in the last few years interact with ≥ 2 pharmacological targets (SERT, 5-HT_{1A}, 5-HT_{1B}, 5-HT_3, 5-HT_7) and have more than 2 mechanisms of action (serotonin transporter inhibition, agonism/antagonism of ionotrophic and metabotrophic receptors) [38].

Drug discovery processes in major depression are mainly planned to include multiple mechanisms of action in the same antidepressant in one drug different mechanisms of drugs as observed in combination therapies in clinical practice. Several controlled clinical studies have in fact demonstrated the possibility of increasing response and remission rates by combining SSRIs with noradrenaline and dopamine reuptake inhibitors (NDRI) such as bupropion. However, such advantages were not confirmed in the recent CO-MED study when considering the increased risk of adverse events [38 39].

Drug discovery processes were initially focused on the development of new multimodal antidepressants that could sinergistically potentiate the three monoaminergic systems (5-HT, NA and DA) with triple inhibitors of monoamine reuptake such as amitifadine, even if preregistration clinical studies have still not provided definitive conclusions on the clinical efficacy of these drugs [40].

With the progressive accumulation of new evidence on the involvement of other neurotransmitter systems such as the glutamatergic and cholinergic [41], preclinical research has focused on the development of the first multimodal antidepressant with multiple monoaminergic targets that can interact with ≥ 2 pharmacological targets (SERT, 5-HT_{1A}, 5-HT_{1B}, 5-HT_3, 5-HT_7) and have more than 2 mechanisms of action (serotonin transporter inhibition, agonism/antagonism of receptors) [38] (Table I).

In the development process, this approach has been largely conservative by attempting to maintain the clinical benefits of SERT inhibition but including at the same

time other pharmacological targets such as 5-HT_{1A} receptors in order to reduce the slow onset of action and improve upon the tolerability profile (and in particular sexual dysfunction). Vilazadone was the first effort to develop a multimodal antidepressant whose pharmacodynamic profile includes inhibition of SERT and partial agonism of 5-HT_{1A} (Fig. 1). However, the initial clinical benefits observed in terms of reduction of the onset of clinical action were not confirmed in later studies, and this drug was also found to be associated with gastrointestinal adverse effects [42 43].

Vortioxetine is the latest candidate among multimodal antidepressants. Its pharmacodynamic profile includes not only inhibition of SERT and partial agonism on 5-HT_{1A}, but also antagonism on 5-HT_3 and 5-HT_7 receptors that allows, for the first time, indirect intervention on the glutamatergic system of the prefrontal cortex which to date has not been targeted with currently used antidepressants.

The development of multimodal antidepressants in recent years, and in particular vortioxetine, has been improved in parallel with advances in understanding the neurobiological basis of depression ("the glutamatergic hypothesis of depression"). In addition, classification systems of psychotropic drugs have been revised in the attempt to renew these systems with new evidence in neuroscience, also considering of the wide spectrum of use of psychotropic drugs in clinical practice if referred to their approved indications.

In the last two years, different studies have been carried out at the ECNP (European College of Neuropsychopharmacology) by Joseph Zohar, David Nutt, Guy Goodwin, in collaboration with Stephen Stahl (International College of Neuropsychopharmacology) and the American College of of Neuropsychopharmacology (Pierre Blier and David Kupfer) in order to propose a new classification system based on mechanism of action, and not only on the use of the older nomenclature based on ATC categories and approved indications. For example, antidepressants are effective not only in treatment of major depression, but also in anxiety disorders. At the same time, antipsychotics are used in the treatment of bipolar disorder and not only in psychoses due to their diverse mechanism of action and neurobiological activity profile. The older ATC nomenclature, therefore, does not describe all the potential clinical applications of this class of drugs [44].

In accordance with the new classification (neuroscience-based nomenclature) recently presented at Berlin at the 27th Congress of the European College of Neuropsychopharmacology (18-21 October 2014), every psychotropic drug can be classified according to the following 4 axes:

- Axis 1: Pharmacologic target and mechanism of action. This axis reflects current knowledge of molecular

TABLE I.
Potential advantages of a multimodal approach in the pharmacological treatment of major depression. *I possibili vantaggi dell'approccio multimodale nel trattamento farmacologico della depressione maggiore.*

- Combination of multiple mechanisms of action in a single antidepressant
- Inclusion of new pharmacological targets and interaction with other neurotransmitter systems (e.g., glutamatergic system) in addition to monoaminergic systems (SERT inhibition)
- Possibility to treat residual symptoms such as cognitive symptoms which are frequent depressed patients with a suboptimal response to SSRIs and SNRIs
- Possibility to use antagonistic activity on receptors involved in adverse effects (e.g. 5-HT_3) and consequent improvement of the tolerability profile

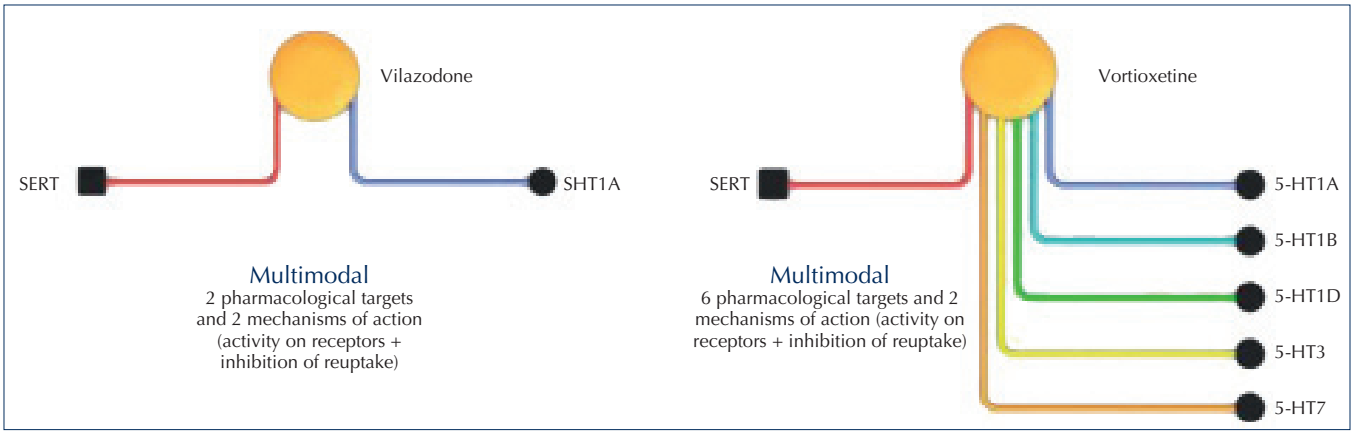


FIGURE 1.
Examples of multimodal antidepressants. *Esempi di antidepressivi multimodali.*

targets and pharmacology and the most accepted hypotheses on its mechanism of action;
- Axis 2: Approved indications. Reports the current therapeutic indications of the drug approved by regulatory authorities (FDA, EMA);
- Axis 3: Efficacy and tolerability. Summarise the evidence on clinical efficacy and most frequent clinical uses, in addition to its tolerability profile and most common adverse effects;
- Axis 4: Neurobiological activity. Describes the main preclinical pharmacology of the drug and primary neurobiological activity on different neurotransmitter systems. In addition, this axis reports, whenever available, relevant clinical data obtained in phase I/II studies.

According to this new nomenclature [45], recent neurobiological understanding of several neuropsychiatric disorders and on the neurobiological activity profile of different psychotropic drugs can be combined in a new system based on mechanism of action that better corresponds to a dimensional approach for a more appropriate clinical use.

In this new scenario, multimodal antidepressants, and in particular vortioxetine, represent a novel opportunity for pharmacological treatment of major depression in light of preclinical and clinical efficacy and possible mechanism of action on multiple psychopathological dimensions (mood, anxiety, cognition) in combination with a good tolerability profile.

Knowledge of the pharmacodynamic profile of vortioxetine thus represents an essential step in understanding the potential advantages of a multimodal approach in pharmacological treatment of depression and the potential use of this drug in clinical practice.

Pharmacodynamic profile of vortioxetine: from development to new pharmacologcal targets

Vortioxetine is an example of a multimodal antidepressant that, in addition to classic inhibition of SERT, is also a full agonist of 5-HT_{1A} receptors, partial agonist of 5-HT_{1B} receptors and an antagonist of 5-HT_{1D}, 5-HT3 and 5-HT_7 receptors (Fig. 1). The drug discovery of vortioxetine is a good example of innovation and serendipity. The initial objective in the development of vortioxetine was to develop a lead compound that combined SERT inhibition with: 1) 5-HT_{1A} agonism to reduce the slow onset of clinical action and minimise side effects related to sexual dysfunction; 2) antagonism of 5-HT_3 to reduce nausea, a frequent side effect with SSRIs during the first few weeks of treatment [46 47].

During development of vortioxetine it was observed that 5-HT_3 antagonism led to further potentiation of the serotoninergic system (extracellular accumulation of 5-HT) in addition to that produced by inhibition of SERT [48]. Moreover, in the initial design of the molecule 5-HT_{1B} agonism was not anticipated, which was later revealed to be important for potentiating the SSRI action of vortioxetine in animal models of depression, and especially antagonism of 5-HT_7 receptors that no other antidepressant had. This rendered vortioxetine unique compared with other antidepressants as a possible positive, indirect modulator of the glutamatergic system [46].

Following the drug discovery process, the pharmacodynamic profile of vortioxetine was characterised by an elevated potential to inhibit SERT with an affinity similar to escitalopram (1.6 nM *vs* 10 nM), along with intrinsic full agonist activity for 5-HT_{1A} receptors, partial agonist activity for 5-HT_{1B} receptors and antagonist activity for 5-HT_{1D}, 5-HT_3 and 5-HT_7 receptors (Table 2, Figure 2) [46 47 49].

If the pharmacodynamic profile and functional activity of vortioxetine is compared in rats and humans it can be observed that vortioxetine has affinity binding values that are similar for the different types of receptors with the exception of 5-HT_{1A} and 5-HT_7 where the affinity is higher in humans (Table II). Preclinical pharmacological studies have considered this difference relevant and adopted a range of doses starting with 0.5 mg/kg, a dose that corresponds, after an acute treatment in rats, to an occupation of 5-HT_3 and 5-HT_{1D} receptors and 50% of SERT, up to doses of 5-10 mg/kg in which vortioxetine fully occupies the 5-HT_{1B}, 5-HT_{1A} and 5-HT_7 receptors [46].

To describe the pharmacodynamic profile of vortioxetine it is necessary to consider the contribution of serotonergic receptors, and in particular 5-HT_{1A}, 5-HT_3 and 5-HT_7, in order to explain the broad spectrum of efficacy of the drug not only in classic animal models of depression, but also in newer preclinical models in which currently-available SSRIs are not efficacious [46]. 5-HT_{1A} receptors have an important role in clinical response to antidepressants in treatment of major depression [50]. As already mentioned, preclinical studies have demonstrated that the difference in the onset of therapeutic action and the rapid modification at the synaptic level of biogenic amines in the acute phase observed after 3-4 weeks cannot be explained by down-regulation of 5-HT_{1A} receptors alone, but with the progressive alteration of other specific signaling pathways (CREB, GSK-3beta, AKT/mTOR), the increased release of neurotrophic factors (e.g. BDNF) and the consequent effects on synaptic plasticity [47 51 52].

5-HT_{1A} receptors are a subgroup of receptors localised at the somatodendritic level of serotonergic neurons that originate at the level of the raphe nuclei as well as at the presynaptic level in the terminations of serotonergic neurons at different areas of the CNS, such as the hippocampus and prefrontal cortex. At the somatodendritic level, 5-HT_{1A} receptors inhibit firing of serotonergic neurons;

TABLE II.
Multimodal activity of vortioxetine: differences in affinity between humans and rats. *L'attività multimodale di vortioxetina: le differenze di affinità tra uomo e ratto.*

	Affinity (nM)	
Receptor	**Rat**	**Human**
5-HT$_3$	1.1	3.7
5-HT$_7$	190	19
5-HT$_{1A}$	230	15
5-HT$_{1B}$	16	33
5-HT$_{1D}$	3,7	54
SERT	8,6	1,6

desensitization and especially down-regulation of 5-HT$_{1A}$ receptors is crucial for the clinical efficacy of antidepressants [50]. In the first phase of treatment with SSRI antidepressants, 5-HT$_{1A}$ receptors are stimulated by elevated levels of 5-HT with consequent inhibition of firing and the possible presence of anxiety symptoms. In succession, 5-HT$_{1A}$ receptors undergo progressive desensitisation and especially down-regulation with consequent recovery and a successive increase in firing of serotonergic neurons. Vortioxetine, due to the combination of full agonism of 5-HT$_{1A}$ and antagonism of 5-HT$_3$ together with classic SERT inhibition, leads to rapid desensitization of 5-HT$_{1A}$ receptors with rapid activation of the serotonergic system compared to SSRIs such as fluoxetine (24 h *vs* 7 days) [46]

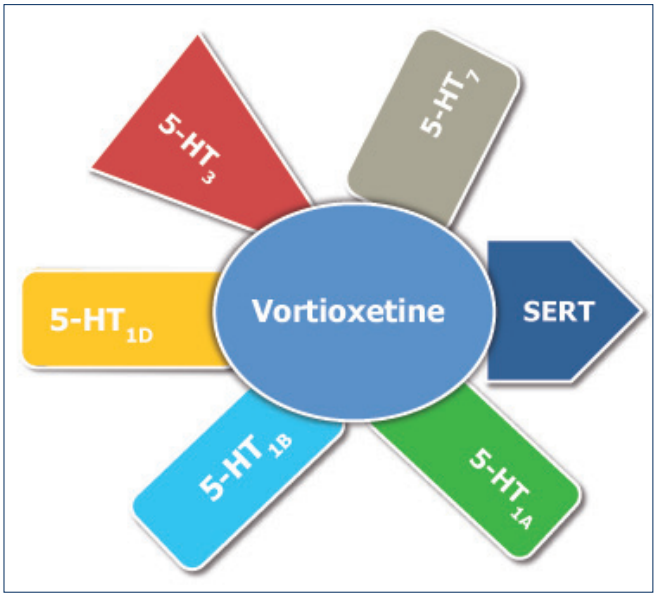
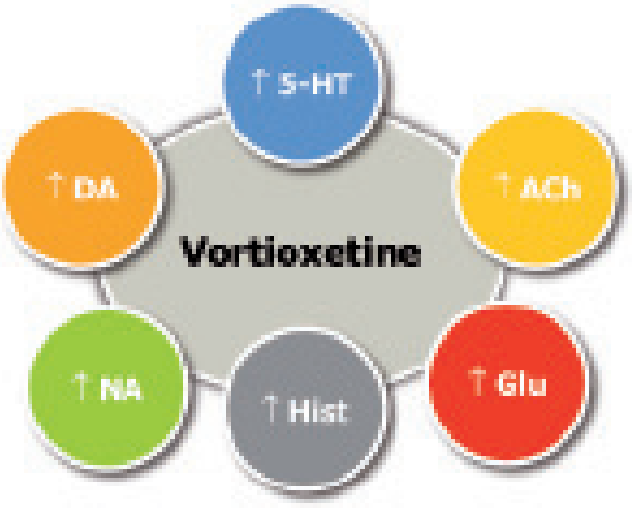


FIGURE 2.
Pharmacodynamic profile of vortioxetine. *Profilo farmacodinamico di vortioxetina.*

[53 54]. It has been hypothesize that the antagonism on presynaptic 5-HT$_{1D}$ receptors, included in the mechanism of action of vortioxetine, could contribute to the potentiation of the serotonergic system since it is known that selective antagonists of 5-HT$_{1D}$ receptors potentiate the increase in extracellular levels of 5-HT induced by SSRIs [55].
It has been demonstrated that the effects of vortioxetine on serotonergic neurons of the raphe depend significantly on antagonism of 5-HT$_3$ receptors [46]. It is already well-known that the combination of 5-HT$_3$ receptor antagonists with SSRIs potentiates the extracellular increase in serotonin in the prefrontal cortex and ventral hippocampus compared with a single treatment with SSRI [48]. It has also been demonstrated in rats that agonists of 5-HT$_3$ receptors such as SR57227 prevent the rapid reactivation of the serotonergic system observed after a long-term administration of vortioxetine at a dose of 5 mg/kg [53]. These pharmacological effects of vortioxetine observed in animal models could lead to a better tolerability profile during the first week of treatment with a reduction in anxiety symptoms associated with inhibition of the serotonergic system induced by SSRIs during the first days of treatment.
A specific feature of the pharmacodynamic profile of vortioxetine is the ability to indirectly potentiate the activity of other neurotransmitter systems involved in the pathogenesis of major depression such as the noradrenergic, dopaminergic, cholinergic, and in particular the glutamatergic system; a major pharmacological target recently studied for the treatment of depression (Fig. 3).
Vortioxetine significantly increases the extracellular levels of noradrenaline (NA) in the prefrontal medial cortex and ventral hippocampus following acute or chronic administration in rats [54]. It is interesting to note that vortioxetine is not associated with a significant inhibition of the noradrenaline transporter (NAT) at either the level of the central or peripheral nervous system; it does not increase the peripheral levels of NA as observed with SNRI antidepressants, which through NET inhibition, can favour the onset of adverse effects such as tachycardia and an increase in arterial blood pressure [57 58]. Recent evidence suggests that vortioxetine indirectly potentiates the NA system at the medial prefrontal cortex and ventral hippocampus due to antagonism of 5-HT$_3$ combined with agonism of 5-HT$_{1A}$ receptors [46]. Antagonism on 5-HT$_3$ receptors leads to a reduced release NA in the locus coeruleus along with a reduced activation of inhibitory presynaptic α_2 receptors and the following increase in firing of noradrenergic neurons starting from the locus coeruleus with a concomitant release of NA in the prefrontal cortex and hippocampus. The agonism on 5-HT$_{1A}$ receptors contributes to potentiation of this effect as it leads to an increase in the extracellular levels of NA in the same areas [46 58].

Vortioxetine, due to its agonist activity on 5-HT_{1A} receptors, also leads to an increase in the extracellular levels of dopamine (DA) in the medial prefrontal cortex at a dose of 5 mg/kg, while it does not influence the activity of the mesolimbic dopaminergic system or the release of DA in the nucleus accumbens [46 54]. Moreover, vortioxetine, in addition to its activity on monoaminergic systems, increases the release of acetylcholine and histamine in the medial prefrontal cortex (Fig. 3).

FIGURE 3.
Direct and indirect effects of vortioxetine on neurotransmitter systems. *Effetti diretti e indiretti di vortioxetina sui sistemi neurotrasmettitoriali.*



SERT: serotonin transporter; 5-HT: serotonin; ACh: acetylcholine; Hist: histamine; NA: noradrenaline; DA: dopamine.

Interaction between the serotonergic and glutamatergic systems: the specific role of vortioxetine

The glutamatergic system plays an essential role in the pathophysiology of major depression and in the pathogenesis of cognitive symptoms in depression [59 60]. The glutamatergic system is considered a relevant pharmacological target for the development of new antidepressants with a better pharmacodynamic profile, especially in the management of treatment-resistant depression [30 59].
In major depression, it has been demonstrated a dysfunction of the glutamatergic system consisting of hyperactivation of ionotropic NMDA receptors for glutamate with an increased release of glutamate correlated with acute stress and possible neurodegenerative phenomena in the prefrontal cortex and hippocampus [28 29]. It has also been shown that first and second generation antidepressants can reduce the release of glutamate, especially after acute stress, and that they can reduce glutamatergic transmission at the levels of NMDA receptors, potentiating AMPA receptors [28].
The discovery of the rapid antidepressant action of ketamine, a non-competitive antagonist of NMDA receptors, in patients with treatment-resistant depression has opened new avenues for the identification of new pharmacological targets and developing new antidepressants that can directly or indirectly modulate the glutamatergic system [61].
Ketamine is an effective drug for therapy of treatment-resistant depression, although it is associated with psychotomimetic effects (hallucinations and perception disorders) and has a high potential for abuse as highlighted by several studies [29]. Moreover, it has been demonstrated that abuse of ketamine may also lead to comprised cognitive function and alteration in thought content [29]. Considering these aspects, it is clear that ketamine cannot be readily used in clinical practice due to issues regarding tolerability and safety. It is thus necessary to develop new antidepressants with serotoninergic action that can also indirectly modulate the glutamatergic system [61].
The serotonergic system influences the glutamatergic system through 5-HT_{1A}, 5-HT_{1B}, 5-HT_3 and 5-HT_7 receptors. Ketamine loses its antidepressant efficacy in animal models following depletion of serotonin, which suggests that the serotonergic system has an essential role in modulation of the glutamatergic system. Multimodal antidepressants such as vortioxetine can modulate the glutamatergic system through interaction with serotonergic receptors including 5-HT_{1A}, 5-HT_{1B}, 5-HT_3 and 5-HT_7 which can regulate the neurobiological effects of the serotonergic system on the glutamatergic system.
Recent studies suggest that vortioxetine, through antagonism of 5-HT_3 and 5-HT_7 receptors, exerts a positive modulation on the glutamatergic system in the prefrontal cortex. This action may lead to an increase in clinical efficacy when treating residual symptoms, such as cognitive symptoms, which are often present in patients with suboptimal or inadequate response to antidepressants finally preventing the achievement of complete remission in clinical practice [61 62]. Similar to ketamine, vortioxetine also selectively activates the Akt/mTOR pathway, unlike SSRIs which inactivate it. Of interest, the Akt/mTOR pathway has an essential role in mediating the synaptic and neurotropic effects of ketamine [29 63]. Moreover, it has been hypothesized that vortioxetine, through antagonism of 5-HT_3 receptors expressed on dendrites of GABAergic neurons, reduces the inhibition exerted by 5-HT_3 on pyramidal glutamatergic neurons in the prefrontal cortex and at the same time inhibits the activity of GABAergic neurons at the level of CA1 region of the hippocampus [61].
In addition, prolonged antagonism on 5-HT_3 receptors leads to the induction of long-term potentiation (LTP), one

of the most important molecular and cellular phenomena underlying learning and memory, as recently observed with vortioxetine in ex vivo hippocampal studies in rats [64]. These studies showed for the first time that vortioxetine prevents the increase of inhibitory postsynaptic currents induced by serotonin at the level of pyramidal cells in the CA1 region of the hippocampus and enhances LTP, events that are not modified by treatment with SSRIs such as escitalopram [64]. Augmentation of LTP by vortioxetine also stimulated neurogenic processes in the subgranular zone of the dentate gyrus in mice within 14 days of treatment in contrast to that observed with fluoxetine, which leads to proliferation and differentiation of neural precursors after only 21 days of treatment [65]. It is interesting to note that vortioxetine, after 14 days at a dose of 20 mg/kg, also leads to significant increases of dendrites lenght and dendritic connections, which are likely related to the selective activation of the AKT/mTOR pathway.

Finally, vortioxetine enhances the glutamatergic system at the level of the prefrontal cortex and hippocampus through antagonism on 5-HT$_7$ receptors [61]. 5-HT$_7$ receptors are located on the soma and the presynaptic terminals of glutamatergic pyramidal neurons that project from the prefrontal cortex to the raphe nuclei, from which serotonergic neurons originate. Moreover, 5-HT$_7$ receptors are expressed on GABAergic interneurons at the level of the prefrontal cortex and hippocampus. The antagonism on 5-HT$_7$ receptors by vortioxetine directly on glutamatergic neurons of the prefrontal cortex leads to an enhancement of glutamatergic transmission towards the raphe nuclei with a subsequent activation of serotonergic neurons [61].

In animal models, it is known that 5-HT$_7$ antagonists enhance the response to SSRIs and improve memory and executive functioning in models of cognitive dysfunction induced by the administration of competitive antagonists of NMDA receptor such as MK-801 or addictive substances such as phencyclidine [61 66]. It is interesting to note that in these animal models synergistic efficacy was seen by combining SSRIs with selective 5-HT$_7$ antagonists [67]. Importantly, vortioxetine combines both of these pharmacodynamic properties in the same molecule.

Taken together, the effects of vortioxetine on the glutamatergic system, neurogenic processes and synaptic plasticity can explain its clinical efficacy in both animal models of depression and in cognitive dysfunction in depressed patients with cognitive deficits [62] or suboptimal response to SSRIs [68]. In particular, the positive modulation of the glutamatergic system in the prefrontal cortex, through antagonism of 5-HT$_3$ and 5-HT$_7$ receptors, is associated with an increased clinical efficacy compared to SSRIs in the treatment of residual symptoms such as cognitive symptoms that prevent the achievement of functional remission in clinical practice.

Preclinical efficacy of vortioxetine in animal models of depression

In recent years, vortioxetine has been extensively studied in animal models of depression, and has shown efficacy as an antidepressant in rodents in the range of 1-10 mg/kg [46]. This has been demonstrated following acute administration in classic behavioural tests such as the forced swim test (both in mice and in Flinders sensitive line rats), the rat social interaction test and the novelty-suppressed feeding test [65]. The efficacy of vortioxetine in these animal models is based on the monoamine hypothesis even after 14-21 days of treatment [65], and is also efficacious in animal models of depression in which SSRIs are ineffective. In particular, it has been demonstrated that vortioxetine is effective in C57 mice that do not respond to SSRIs [69] and in an animal model based on the GABAergic hypothesis of depression known as progesterone withdrawal. In this model, the abrupt discontinuation of progesterone administration in the rat following a long-term treatment (21 days) leads to the onset of anxiety, irritability and a depressive phenotype with anhedonia and social withdrawal. The administration of vortioxetine has an antidepressant effect as measured by the forced swim test, in contrast to that observed with fluoxetine or duloxetine in this model [70 71].

Due to its multimodal action and its ability to interact with multiple targets, vortioxetine has an antidepressant effect in animal models after a sub-chronic treatment at a dose of 5 mg/kg, a dose that is associated with only a partial occupation of SERT (40%). It can be hypothesize, in fact, that agonism on 5-HT$_{1A}$ receptors in combination with antagonism on 5-HT$_3$ receptors, is essential for increasing the efficacy of vortioxetine compared with SSRIs in animal models where SSRIs and SNRIs are ineffective.

In recent years, research in psychopharmacology has focused on improving the translational value of animal studies with the aim of developing a model with an increased predictive value [30]. The main problem, in fact, is that of reproducing, within the limits of the large differences between rodents and humans, behavioural phenotypes that have the same neurobiological basis of symptoms such as cognitive deficits (attention, memory and executive functioning) that still represent the most relevant unmet needs in the pharmacological treatment of depression.

Animal models of cognitive dysfunction: the unique mechanism of action of vortioxetine

Vortioxetine is the first example of an antidepressant that has been widely studied not only in animal models of depression, but also in all the newer models of cognitive dysfunction (and in particular attention, memory and executive functioning) where SSRIs such as fluoxetine and

escitalopram are ineffective [72]. It is interesting to note that the increased spectrum of preclinical efficacy of vortioxetine in animal models of depression was also seen in terms of clinical efficacy in treatment of cognitive deficits in MDD [62]. Among the main mechanisms involved in this effect, it is believed that enhancement of the cholinergic and glutamatergic systems in the hippocampus and activation of the dopaminergic system in the prefrontal cortex arising from the multimodal action of vortioxetine are most relevant since these neurotransmitters have a role in cognitive functions such as attention, memory and executive functioning [46 72]. Study of EEG patterns in rodents has confirmed that there are relevant differences between vortioxetine and second-generation antidepressants (SSRIs and SNRIs) in terms of general neurobiological effects, and in particular on the state of vigilance [72]. Quantitative analysis of the EEG in the prefrontal cortex in rodents has a good translational value and is a validated method to predict EEG patterns in man [72]. It is known, in fact, that the activity on theta and gamma waves is directly correlated with memory encoding and retrieval, whereas alpha and gamma waves are mostly associated with attention [73]. A close correlation between the antidepressant effects in the quantitative analysis of EEG at the prefrontal cortex and the effects of these drugs on cognitive function has been demonstrated [72]. In particular, it has been observed in rats that vortioxetine, even at a dose of 5 mg/kg administered in acute (corresponding to 80% occupation of SERT), is associated with a completely different EEG pattern than either escitalopram (2 mg/kg) or duloxetine (10 mg/kg) administered at doses that lead to 80% occupation of SERT (and thus equivalent doses in preclinical terms) [72]. Vortioxetine increases the activity of alpha, theta and gamma by 25-60%, in contrast to escitalopram and duloxetine which reduce their activity. The authors of that study also demonstrated that the effects of vortioxetine are mediated by the 5-HT_{1A}, 5-HT_3 and 5-HT_7 receptors [73]. These data, together with that of Dale et al. [64] on the enhancement of LTP, can explain the effects of vortioxetine in animal models of cognitive dysfunction [72].

In fact, vortioxetine has been demonstrated to potentiate processes of acquisition and retention of memory (including visuospatial) in many rodent models [46 72]. In particular, vortioxetine reverts memory deficits in the rat induced by serotonin depletion following administration of selective inhibitors of tryptophan hydroxylase [74 75]. The effects of vortioxetine have been observed in the novel object recognition test even at low doses (0.1 mg/kg) in which 80% of 5-HT_3 receptors are blocked. In the same animal model, the authors demonstrated that the pro-cognitive action of vortioxetine is related not only to antagonism of 5-HT_3 receptors, but also to agonism of 5-HT_{1A} receptors [74]. In the same animal model, SSRIs such as escitalopram and SNRIs such as duloxetine are not able to 'correct' memory deficits induced by serotonin depletion [75]. Therefore, occupation of SERT does not seem to be relevant in 'rescuing' cognitive deficits in animal models, and the multimodal activity of vortioxetine acquires provides an added value when considering its pharmacodynamic profile [46 75]. Moreover, in adult rats, vortioxetine is associated with recovery of learning that has been compromised by treatment with selective inhibitors of tryptophan hydroxylase or exposition to chronic stress (i.e. cold) [76]. Lastly, administration of vortioxetine for 4 weeks in older C57BL/6 mice (12 months) leads to improvements in visuospatial memory, whereas fluoxetine, even at high doses, is ineffective in the same model [69].

Vortioxetine has also been demonstrated to be effective in a preclinical rat model of dysfunction of attention and executive function induced by subchronic administration of phencyclidine (PCP, 5 mg/kg for 7 days) [46]. This is an important model for validation of the hypothesis that the glutamatergic action of vortioxetine is relevant to its action. In the PCP model, in fact, the glutamatergic system is compromised at the level of the prefrontal cortex. Vortioxetine is able to revert these effects, resulting in improvement in tests of attention and executive function even at a dose of 3 mg/kg administered either chronically or acutely [46 77].

Overall these data (Table III) can explain why the broad spectrum of preclinical efficacy seen with vortioxetine in animal models of cognitive dysfunction are confirmed in controlled clinical studies where vortioxetine has been shown to be effective in treatment of cognitive deficits in major depression [62].

Pharmacokinetic profile of vortioxetine

Pharmacokinetic studies in healthy volunteers in preregistration studies showed that vortioxetine has a linear pharmacokinetics over a wide dose range from 2.5-60 mg/day following a single administration [78]. Vortioxetine has a half-life of 66 hours and steady-state plasma levels are reached in about 2 weeks (12-14 days). The absolute bioavailability of vortioxetine is 75% after oral administration and its absorption is not influenced by food. In addition, vortioxetine shows an high level of plasma proteins binding (98%; Table IV) [79].

The main pharmacokinetic parameters of vortioxetine are a T_{max} of 7-8 hours (time needed to reach a maximal plasma concentration after a single administration) and a C_{max} of 9 ng/ml after a dose of 5 mg/day and 33 ng/ml after a dose of 20 mg/day (Table IV). The starting dose is 10 mg/day in a single administration with the possibility to increase the dose to 20 mg/day after one week of treatment, or reduce it to 5 mg/day depending on the individual response [79].

Vortioxetine is metabolized by oxidation via multiple CYP450 isozymes (CYP2D6, 3A4/5, 2C19, 2C9 and 2B6) and the following conjugation with glucuronic acid [80]. CYP2D6 is the major isoenzyme involved in the phase I metabolism of vortioxetine [81]. Plasma concentrations of vortioxetine are about twice in CYP2D6 poor metabolizers compared to extensive metabolizers [79]. The maximum dose in poor metabolizers is 10 mg/day. The metabolites of vortioxetine [main metabolite 3-methyl-4-(2-piperazine-1-yl-phenylsulphanyl)-benzoic acid] do not have antidepressant activity, do not cross the blood-brain barrier and are thus not pharmacologically relevant [46]. No relevant differences have been observed in the main pharmacokinetic parameters in relation to gender or in the presence of reduced hepatic or renal function [79].

It is important to underline that vortioxetine, in contrast to several SSRIs (fluoxetine, paroxetine, fluvoxamine) and SNRIs (duloxetine), does not inhibit several isoenzymes of CYP450 (CYP2D6, 3A4/5, 2C19, 2C9) and thus does not have any clinically relevant drug interactions.

Polypharmacy is a common and frequent practice in psychiatry due to treatment of comorbidities or as add-on therapy. The availability of different classes of drugs has also increased the probability of pharmacodynamic and pharmacokinetic interactions with consequent risk of morbidity and mortality, especially in the elderly population. Detailed knowledge of clinically-significant pharmacological interactions is therefore needed on the basis of the available evidence [82]. SSRIs an heterogeneous class of antidepressants with substantial differences in pharmacodynamics and pharmacokinetics. Some SSRIs such as fluoxetine, paroxetine and fluvoxamine can modify the plasma concentrations of other psychotropic drugs by inhibiting CYP450 isoenzymes, thus causing clinically-relevant pharmacological interactions [82].

According to this scenario, vortioxetine has an advantage compared to SSRIs because it does not modify the activity of CYP450 isoenzymes, and thus does not cause clinically-relevant pharmacological interactions [60]. It is nonetheless important to specify that inhibitors of CYP2D6 such as bupropion or inhibitors of CYP3A4 such as fluconazole and ketoconazole can increase the AUC and C_{max} of vortioxetine (respectively +128% and 114% for bupropion, +46% and +15% for fluconazole, +30% and +26% for ketoconazole) [60]. However, these interactions are not clinically relevant considering the broad therapeutic index of vortioxetine, even if in such cases appropriate dose reduction of vortioxetine should be considered in case of interaction with inducers of CYP3A4 such as rifampicin that reduce the AUC and C_{max} (respectively -73% and -51%); in this case a dose increase of vortioxetine can be considered [81].

Overall these data suggest that vortioxetine has a favourable pharmacokinetic and tolerability profile char-

TABLE III.
Summary of evidence in preclinical studies [25 41]. *Sommario delle evidenze negli studi di farmacologia preclinica [25 41].*

Target	Action	Results in preclinical models
5-HT_3	Antagonism	Increase in the effects of SSRIs / SNRIs Enhancement of extracellular increase of 5-HT in the medial prefrontal cortex and ventral hippocampus compared to monotherapy with SSRI in rats Increase in extracellular levels of noradrenaline in the medial prefrontal cortex and ventral hippocampus in rats Positive modulation of the glutamatergic system in the prefrontal cortex Inhibition of GABAergic neurons at CA1 in the hippocampus of rats and augmentation of LTP Procognitive effects in rats depleted of 5-HT and improvements in memory and executive function
5-HT_7	Antagonism	Antidepressant and anxiolytic properties Potentiation of the antidepressant effects of SSRIs in animal models of depression Positive modulation of the glutamatergic system in the prefrontal cortex Improvement of memory and executive function in animal models of cognitive dysfunction
5-HT_{1D}	Antagonism	Enhancement of the extracellular increase of 5-HT compared to monotherapy with SSRIs
5-HT_{1B}	Partial agonism	Potentiation of the antidepressant effects of SSRIs in animal models of depression
5-HT_{1A}	Agonism	Antidepressant and anxiolytic properties Acceleration of desensitization of somatodendritic 5-HT_{1A} autoreceptors with a more rapid reactivation of the serotonergic system in animal models Increase in extracellular levels of dopamine and noradrenaline in the medial prefrontal cortex Procognitive effects in rats following depletion of 5-HT
SERT	Inhibition	Antidepressant and anxiolytic properties in animal models

TABLE IV.
Pharmacokinetic profile of vortioxetine. *Profilo farmacocinetico di vortioxetina*.

Parameter	Vortioxetine
Oral bioavailability	75%
Half-life	66h
T_{max}	7-8h
C_{max}	9 ng/ml (5 mg/die); 18 ng/ml (10 mg/die) 33 ng/ml (20 mg/die)
Plasma binding	98%
Metabolism	*CYP2D6*, 3A4/5, 2C19, 2C9 and 2B6
Drug interactions	*Vortioxetine does not inhibit CYP450 isozymes and does not have any pharmacologically relevant drug interactions* Does reduction is needed in case of co-administration with bupropion, fluconazole or ketoconazole, while dose increase may be needed in case of co-administration with rifampicin
Starting dose	10 mg/die
Dose adjustments	Can be increased (up to 20 mg/day) or decreased (5 mg/day) after 1 week
Administration	Once daily

acterized by the absence of sexual adverse events and weight gain [79].

Conclusions

Multimodal antidepressants are a new psychopharmacological tool for the treatment of major depression. This new pharmacological class includes agents with antidepressant activity which have multiple mechanisms of action. These drugs interact with multiple pharmacological targets thereby modulating several neurotransmitter systems that have not been addressed until now in treatment of major depression, such as glutamatergic, dopaminergic and cholinergic systems. Vortioxetine is an example of a multimodal antidepressant that, in addition to classic inhibition of SERT, also acts as a full agonist on 5-HT_{1A} receptors, partial agonist on 5-HT_{1B} receptors and antagonist on 5-HT_{1D}, 5-HT_3 and 5-HT_7 receptors.
All the evidence presented in this review that vortioxetine has a broad spectrum of efficacy not only in classic animal models of depression, but also in all the newer animal models of cognitive dysfunction (especially memory and executive function). In particular, vortioxetine is the first example of a multimodal antidepressant that, due to its multiple mechanisms of action in addition to SERT inhibition, has been shown to be effective in all animal models of depression and cognitive dysfunction where SSRIs such as fluoxetine and escitalopram and SNRIs such as duloxetine are ineffective [46]. The multiple pharmacological effects of vortioxetine associated with a multimodal approach provide a broad profile of clinical efficacy on multiple psychopathological dimensions (mood, anxiety, cognition) together with a good tolerability profile charcterized by the absence of sexual adverse effects without a significant weight gain [46 79].

Conflict of interests
Filippo Caraci, in relation to the issues treated in the last three years, was a consultant and/or speaker at symposia organized by Lundbeck, Eli-Lilly, Otuska, Grunenthal, Janssen.
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