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SOCIETÀ ITALIANA DI PSICHIATRIA

EVIDENCE-BASED PSYCHIATRIC CARE

OFFICIAL JOURNAL OF THE ITALIAN SOCIETY OF PSYCHIATRY

Contents

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Information for Authors including editorial standards for the preparation of manuscripts

Evidence-based Psychiatric Care, a quarterly on line, open access journal, is the Official Journal of the Italian Society of Psychiatry (SIP).

The journal publishes contributions in the field of psychiatry in electronic format (PDF/HTML) and in English, in the form of regular articles, reviews, short articles, case reports, letters to the editors and commentaries.

- The material submitted should not have been previously published, and should not be under consideration (in whole or in part) elsewhere and must conform to the current regulations regarding research ethics. If an experiment on humans is described, a statement must be included that the work has been performed in accordance with the principles of the 1983 Declaration of Helsinki. The Authors are solely responsible for the statements made in their paper, and must specify that consent has been obtained from patients taking part in the investigations and for the reproduction of any photographs, and report the approval of local ethic committee or institutional review board. For studies performed on laboratory animals, the authors must state that the relevant national laws or institutional guidelines have been adhered to.
- For the publication of each article, a contribution will be asked to the authors for covering the costs of publishing services (technical editing, page layout, tables, diagrams and optimization, management, coordination of contacts with authors for the production of printed version) and to initiate and manage the paperwork for the indexing of the journal in the main international index (Scopus, Psychinfo, Excerpta Medica, Index Medicus, Current Contents).
- For authors who are regular members of the SIP, the contribution will be EUR 200,00 plus VAT for regular or short article, 150 plus VAT for case report, for non-members the contribution will be EUR 250,00 plus VAT for regular or short article, 200 plus VAT for case report. The same fee is applied for articles by multiple authors, the majority of whom are not SIP members.

Conflict of Interests. In the letter accompanying the article, Authors must declare whether they obtained funds or other forms of personal or institutional financial support – or if they are under contract – from Companies whose products are mentioned in the article. This declaration will be treated by the Editor as confidential, and will not be sent to the referees. Accepted articles will be published accompanied by a suitable declaration stating the nature of the financial sources.

Only papers that have been prepared in strict conformity with the editorial norms outlined herein will be considered for publication. Eventual acceptance for publication is conditional to the results of a peer review process, consisting of a critical assessment by experts in the field and implementation of any changes requested, and the final decision of the Editor.

General instructions

- Software and text: please save files in .DOC, .RTF or .DOCX format.
- Illustrations: a) send pictures in separate files from text and tables; b) software and format: preferably send images in .TIFF or .JPEG or .PDF format, resolution at least 300 dpi (100 x 150 mm).
- The text must be written in English.
- The first page of the manuscripts must contain the names of the Authors and of the Institute or organisation to which each Author is affiliated; the name, mailing address, telephone and fax numbers of the Author to whom correspondence and galley proofs should be sent; a set of keywords.
- Tables must be limited in number (the same data should not be presented twice, in both the text and tables), typewritten on separate pages, and numbered consecutively with Roman numerals. In the text and legend to the tables, Authors must use, in the exact order, the following symbols: *, †, ‡, §, **, ††, ‡‡ …
- Figures: please strictly follow the abovementioned instructions.
- The references must be identified in the text by Arabic numbers in upper script and listed at the end of the manuscript in the order of citation. In case of papers by more than 5 Authors, the first 3 Authors should be indicated, followed by et al.
- Journals should be cited according to the abbreviations of Index Medicus.

Examples of the correct format for bibliographic citations

Journal articles:

Schatzberg AF, Samson JA, Bloomingdale KL, et al. T*oward a biochemical classification of depressive disorders, X: urinary catecholamines, their metabolites, and D-type scores in subgroups of depressive disorders*. Arch Gen Psychiatry 1989;46:260-8.

Books:

Kaplan HI, Sadock BJ. *Comprehensive textbook of Psychiatry.* Baltimore: Williams & Wilkins 1985.

Chapters from books or material from conference proceedings:

Cloninger CR. *Establishment of diagnostic validity in psychiatric illness: Robins and Guze's method revisited.* In: Robins LN, Barret JE, editors. The validity of psychiatric diagnosis. New York: Raven Press 1989, pp. 74-85.

- Acknowledgements and the citation of any grants or other forms of financial support should be provided at the end of the paper, after the list of references.
- Notes to the text, indicated by asterisks or similar symbols, should appear at the bottom of the relevant page.
- Mathematical terms and formulae, abbreviations, and units of measure should conform to the standards set out in Science 1954;120:1078.
- Drugs should be referred to by their chemical name; the commercial name should be used only when absolutely unavoidable (capitalising the first letter of the product name and giving the name of the pharmaceutical firm manufacturing the drug, town and country).
- Authors are required to correct and return galley proofs of their paper within 4 days of receipt.

Categories of papers

Manuscripts will be organized in five main categories. Namely:

1. **Regular articles and reviews** (which may also include invited articles). Text length: 18.000 characters or more, with spaces, excluding summary, tables and/or figures and references. The text of regular articles should be subdivided into the following sections: Summary, Introduction, Materials and methods, Results, and Discussion and Conclusions.
2. **Short articles**: this space is dedicated to brief communications of clinical and experimental data and to preliminary data of ongoing research of particular interest. Text length: no more than 12.000 characters, with spaces, including summary, figures and/or tables (no more than 4), and references (max 15).
3. **Meet-the-expert**: in which a well-reputed clinician and/or researcher will provide a short evidence-based review related to an explicit issue.
   - Reviews, articles (both regular and short), and meet-the-expert should contain a window reporting the main implications for psychiatric care that derive from the data presented in the publication.
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4. **Case reports**: in which original experiences related to individual or few subjects are described. Text length: about 4.000-5000 characters, with spaces. Max 1 figure or table and no more than 5 references.
5. **Letters to Editors and Comments concerning articles or reviews published in the Journal**: text length: about 2.000-3.000 characters, with spaces. Max 1 figure and/or table and no more than 5 references.

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EVIDENCE-BASED PSYCHIATRIC CARE: THE WHYS

Emilio Sacchetti, Claudio Mencacci

Editors-in-Chief,
Evidence-Based Psychiatric Care

At first glance, the premises for a new psychiatric journal could appear weak.

Surfing the NET, each of us may indeed immediately figure out how large is the availability of dedicated journals in the area of psychiatry and allied disciplines. The results relative to some of the most popular databases are paradigmatic in this context: for example, on December 2014, PsychINFO® covered 2562 journals, InCites™ included 338 journals under the broad rubric "psychiatry and psychology", and the application to PubMed® of the keyword "psychiatry" selected 559 journals. Furthermore, at the same date, the Journal Citation Reports identified 136 psychiatric journals with impact factor.

Despite the unfavorable premises descending from this crowded scenario, we are persuaded that Evidence-based Psychiatric Care may stands on its own within the psychiatric community. Three main independent considerations support our expectation.

The first consideration is that Evidence-based Psychiatric Care will permit to fill a relevant gap: the fact that the Italian Psychiatric Society has been for many years orphan of an official journal. This situation appears hardly acceptable considering the past and the present role of our Society. Having origins that trace back to 142 years ago, the Italian Psychiatric Society began at the same time as the unity of Italy and the foundation of the German Society of Psychiatry and followed only of a few decades the starting of the corresponding American, British, and French associations. Furthermore, having 8.500 members, the Italian Psychiatric Society rightly enters in the list of the most representative national psychiatric association.

The second consideration comes from the coexistence of two opposing realities: on the one hand, the transfer of information from the experimental to the clinical setting that frequently results neither trivial nor automatic because of marked context differences and, on the other hand, the fact that generalizability of the results outside the original experimental setting represents a topic only minimally considered in current literature. Given the relevant potential of negative repercussions for clinical routine that descend from this gap, a journal as Evidence-based Psychiatric Care primarily aimed to promote a good clinical practice sustained by scientific evidence must be viewed as recommendable. Consequently, controlled clinical trials, real-world naturalistic studies, guidelines, expert opinions, and societal position papers consistent with this mission will have a priority in the journal.

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The third consideration is that the privileged contents of Evidence-based Psychiatric Care could hopefully open the doors also to authors and readers outside the inner, largely academic circle of the habitué of scientific journals. The decision to offer a completely free open-access to the journal and to require low price publication fees embodies the editorial policy to retain new researchers and new readers in a period, as the present, dominated by paucity of economic resources.

However, the proof of the pudding is in the eating.

THE BIRTH OF ITALIAN SOCIETYOF PSYCHIATRY

Paolo Francesco Peloso

Mental Health Department of Genoa, Italy

Abstract

The "Meetings of the Italian Scientists" began more than 40 years before the Italian unification and offered important opportunities to Italian psychiatrists to discuss their work and research. After unification, at the Meeting held in Rome in 1873, a project of scientific association of the Italian alienists was formed, the "Società Freniatrica Italiana", with the aim of "increasing psychiatric studies, progress in the institutions of asylums, and protection and benefit of the insane". In 1932 the association changed its name in "Società Italiana di Psichiatria" (Italian Society of Psychiatry). The following year, the new Society held its first Congress in Imola. In the second part of this paper, the history of the Society together with that of Italian psychiatry and society during the 20th century is briefly remembered, along with the two World Wars, Fascism, the progressive submission of Psychiatry to Neurology, the decay of the situation of inmates inside hospitals, the approval of Law 238 in 1976 which marked the independence of Psychiatry from Neurology and the dialectic encounter with the reform movement leaded by Franco Basaglia until the approval of Law 180 in 1978, which established the closure of psychiatric hospitals in Italy and the organization of an original model of care in the community.

The birth of the Italian Society of Psychiatry and its premises

The first "Riunione degli Scienziati Italiani" (Meeting of Italian Scientists) was held in Pisa in 1839, more than 20 years before the unification of Italy, on the initiative of Prince Carlo Luciano Bonaparte (1803–1857), under the patronage of Grand Duke Leopold II of Tuscany. Medicine was one of 6 areas in which debate took place. After the first reunion, later meetings were held in Turin (1840), Florence (1841), Padua (1842), Lucca (1843), Milan (1844), Naples (1845), Genoa (1846) – where a classification of mental disorders on the basis of phrenology was discussed – Venice (1847). They took so place in all the main pre-unification States, with the exception of the Papal State, which had a suspicious attitude towards them. Initially there were a few hundred participants, which grew to exceed 1,600. Many psychiatrists belonging to the first Italian generation took part, including Benedetto Trompeo (1796(7)-1872) from Turin, Biagio Miraglia (1814-1885) [1] and Timoteo Riboli (1808-1895) from Naples, Pier Francesco Buffa (1813-1844) from Genoa, and psychiatric issues were often debated [2,3].

With the wars and turmoil of 1848–49 the first round of meetings was suspended, and resumed only one year after the unification of Italy with Siena (1862), where the psychiatrists discussed the foundation of an Italian psychiatric society and illustrated a proposal for a law on psychiatric assistance. Other meetings took place in Rome (1873), three years after its conquest by the Italian army, and Palermo (1876). How-

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FIGURE 1.
Benedetto Trompeo.

ever, before the unification they constituted the most important opportunity for international comparisation between Italian Scientists of the peninsula and contained an implicit political reference to it. Now, it was not only the fact that the meetings had lost, by the end of the Risorgimento, their original and politically explosive character to determine their crisis. In reality, also it was the fact that, as remarked by Andrea Verga (1811–1895) [4] at the meeting of Rome, the evolution of science and the rise of its devotees made it necessary that Italian scientists continued to cultivate their fields by accepting the fragmentation of knowledge, and maintaining the same spirit but working in different fields independently from one other.

In fact, on the occasion of the XI Meeting of Rome, from 23 to 28 October 1873, the first encounter between psychiatrists aimed towards the establishment of a scientific society in the field of psychiatry – similar to what had already occurred in the UK (1841), United States (1844), France (1852) and Germany (1864) – was held. A first attempt in this direction, with the Società Frenopatica Italiana founded by Miraglia at Aversa in 1861, was exhausted after a few years: at the meeting of Siena this attempt failed. For this reason, the "Archivio italiano per le malattie nervose e più particolarmente per le alienazioni mentali" (Italian Archive for Nervous Diseases, and in particular for mental alienations), founded in Milan by Verga in 1852 as an "Appendice psichiatrica alla Gazzetta Medica Italiana" (Psychiatric Appendix to the Italian Medical Journal), published an invitation in September 1873 to the Italian alienists to participate the following month at the meeting in Rome.

On 23 October 1873, a dozen stakeholders was present, including Verga and the psychiatrists Carlo Livi (18231877) from Siena [5], Clodomiro Bonfigli (1838–1909) from Ferrara, Giuseppe Girolami (1809–1878) from Rome, Cesare Lombroso (1838-1909) from Pavia [6], Gaetano Cappelli from Lucca, Paolo Fiordispini from Rome, Antonio Michetti (1829–1909) from Pesaro and Giuseppe Neri from Perugia. Apart from Verga, they were mainly from central Italy, but others joined even if absent: Serafino Biffi (1822–1899) from Milan, Stefano Bonacossa (1804–1878) from Turin, Agostino Sbertoli from Pistoia, Francesco Pignocco from Palermo, Augusto Tamburini (1848–1919) [7] from Reggio Emilia, Roberto Adriani from Perugia and Miraglia. The architect Francesco Azzurri (1827–1901), who projected the asylum of Santa Maria della Pietà in Rome and those of Siena and Alessandria, the physicians Giulio Bastianelli and Clito Carlucci (1810–1879), a protagonist of the Risorgimento and first Rector of the University of Rome after the unification, were also present. Once the intention of establishing a scientific society in the field of

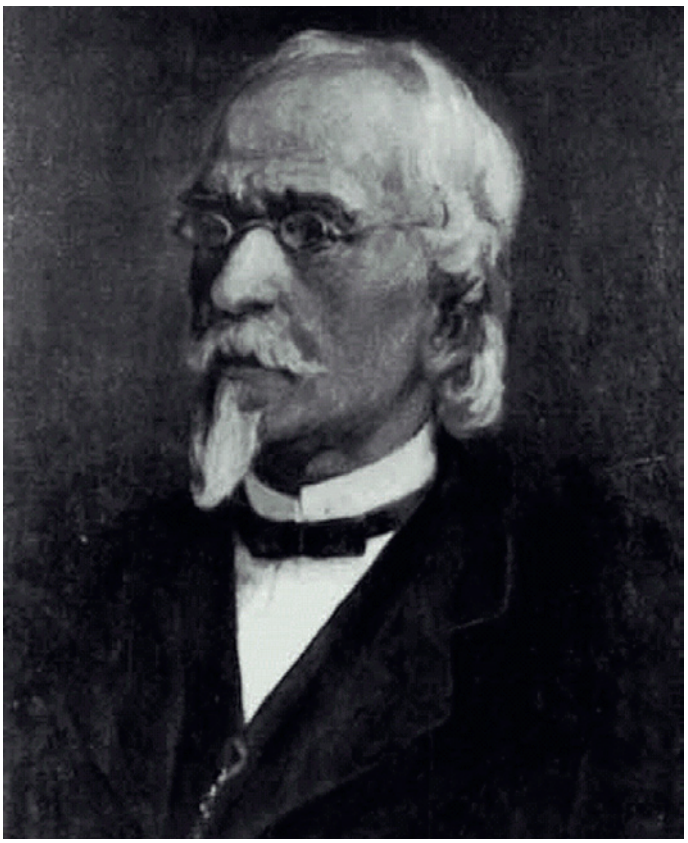

FIGURE 2.
Andrea Verga.

psychiatry was verified, the first issue addressed was the delimitation of its object of study, and consequently its name.

A first hypothesis for the name was 'Medical-psychological Society', using the French example to also include the philosophers engaged in psychology. This hypothesis was rejected by the majority; the medical nature of the society was so established, and the discussion was between psychiatry, with reference to the Greek concept of "psyche", and "freniatria", with reference to that of "fren". The latter hypothesis was preferred because – as confirmed by Livi two years later when he was choosing a title for the new scientific journal of the mental hospital in Reggio Emilia – it was more suited to represent the physical and moral character (i.e. organic and psychological) of the discipline. The Society was thus called "Società Freniatrica Italiana" (SFI). Finally, the proposal to open the domain of the new Society to forensic medicine, advocated by Livi and Lombroso, was rejected.

The Statute was unanimously approved, in which art. 1 established the aims of the Society: "the increase of psychiatric studies, progress in the institutions of asylums, protection and benefit of the insane". It was agreed that the alienists present were considered the founding members, that the members would meet at a congress every 3 years and that the first congress, where 100 psychiatrists participated, would take place the following year in Imola. Verga was acclaimed first president, a three-year term assignment, flanked by Biffi, who would succeed him as president in 1891, in the office of secretary-treasurer. The new Society was endowed with a periodical, and the Archive was then subtitled "Organ of the Società Freniatrica Italiana".

The two main themes discussed were that of the classification and statistics of mental diseases and the need for a national law in the field of psychiatric assistance. There was no time to discuss a third issue, that of forensic asylums, which was postponed until the congress at Imola.

Those days of October 1873 now seem very far away because two years ago the XLVI congress was held in Milan, and to keep track of them is not common in today's debate, with little exception [8,9]. Indeed, the issues discussed (nosology, statistics, law, forensic hospitals) are astonishingly similar to those on the agenda of our Society today.

We cannot say that our Society has always remained faithful in the threefold mandate to work on the progress of psychiatric studies, the improvement of assistance and the protection and benefit of the patients. However, we believe that this threefold aim, adopted many years ago by a generation of psychiatrists who in their youth were hardened by the bitter epics of the Risorgimento and sprouted from the root of the pre-unification Meetings of Italian Scientists [10], witnessed close connection between the psychiatric question and the issue of freedom, democracy and civil progress in the history of Italy [11-13], and remains a commitment and challenge for today's psychiatrists.

Notes for a short history of the SIP from its origin to Law 180 of 1978

In 1896, Tamburini, who is still remembered for his studies of clinics [14] and was very active in the issue of organizing the asylums, became president of the SFI. With the transition from the 19th to the 20th century, the interest of psychiatrists was increasingly moving from the management of care in the asylum to neurological and histological research. The subordination of psychiatry to neurology, which ended only in the 1960s, began in that moment. In 1907, this overwhelming interest in issues of neurology led many leaders of the SFI to create the Italian Society of Neurology, whose first president was Leonardo Bianchi (1848–1927) [15]. In the same years, University

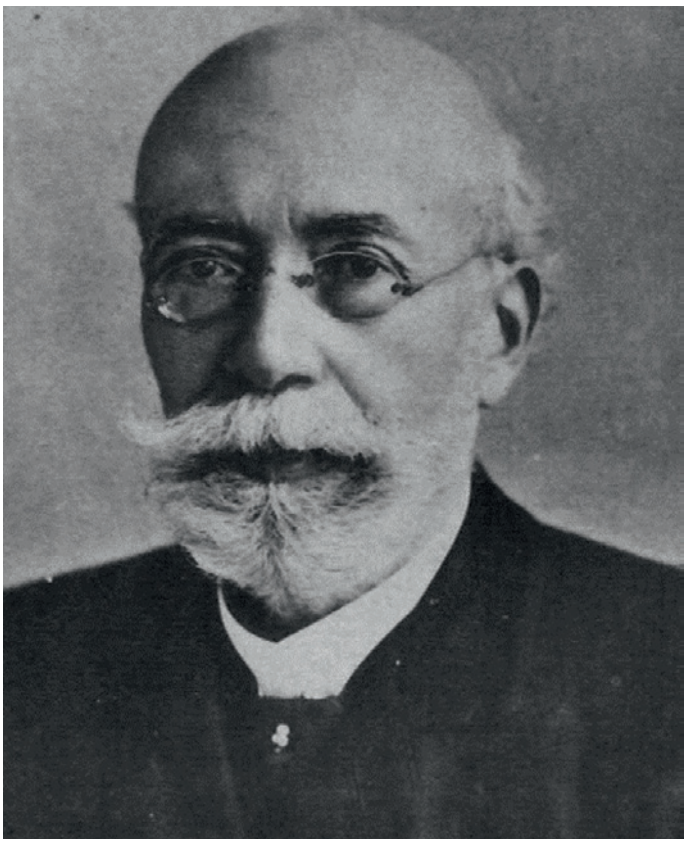

FIGURE 3.
Augusto Tamburini.

Chairs of Psychiatry were disjoined by the Directions of asylums, and both the prestige of the discipline and the quality of assistance were damaged by that separation.
In 1904, Law 36 regulating the functioning of asylums and the assistance of the insane was approved. The leadership of the SFI, and particularly Bianchi, was very active. Hoping to put a stop to the constant increase of inmates, it stated that only the alienated "dangerous to themselves and others or of public scandal" were to be hosted in an asylum, while others remained in the custody of their families or municipalities. Accepting the wishes of the SFI, the absolute authority of the Director on the other psychiatrists and the administrative staff was also strengthened. Next autumn, the 12th Congress of the SFI was held in Genoa, and Ernesto Belmondo (1863–1939) from Padua intervened on the issue of physical restraint, arguing the need to adapt the politics of no restraint in Italy, already pursued in Britain and Germany, and some still very interesting arguments were proposed [16]. His position was partially accepted by the SFI and affected the implementing regulation of the law, approved in 1909.
During the years of World War I, the commitment of psychiatrists in selection of recruits and in diagnostic evaluation and treatment of soldiers who showed symptoms of mental illness was remarkable. A complex organization was predisposed, involving many asylums, and led by Tamburini with the rank of Medical General. A promising young psychiatrist, Gaetano Perusini (1879–1915), who had worked with Alzheimer in the neuro-histological study of dementia, died in a field hospital at the front.
During the presidency of Tamburini, the leadership of the SFI also had to cope with the complaints of the gynaecologist Luigi Maria Bossi (1858–1919), supporter of a bizarre thesis on the genital origin of female mental illnesses, on several interesting topics such as the weakness of the foundations of psychiatric diagnosis, the poor quality of life of inmates in asylums, the attitude of closure of psychiatrists to the possibility of continuing care at home and their attitude of hostility and self-sufficiency with the other branches of medicine and the general hospital [17].
When Tamburini died in 1919, Enrico Morselli (1852–1929) [18], from the University of Genoa, was elected president in a regime of substantial continuity. During his presidency, the SFI discussed psychoanalysis, and after an initial position of opening later rejected it. In the same period, the issue of sterilizing patients and of killing chronic ones considering human life without value, two theses which had supporters in both North European and North American scientists, were strongly rejected by Morselli [19] and by the other leaders of the Society after him, including his successor Arturo Donaggio (1868–1942). Morselli joined the Fascist movement and in 1925 signed the "Manifesto of Fascist Intellectuals" promoted by the philosopher Giovanni Gentile, but was able to protect the SFI to the intrusion of the regime, and there is almost no trace of political influence in the Proceedings of the Congresses during his decade.
This changed after his death, when the regime's attempt to influence Italian social life in all its aspects became more insistent. In 1932 under the presidency of Donaggio from the University of Modena, with a referendum among members the anachronistic name of the Society was changed to Società Italiana di Psichiatria (SIP, Italian Society of Psychiatry). This step sanctioned the break with the generation of the founders (that of the alienists or "freniatri" of the 19th century), and for the SIP this was the true turning point to the new century. His figure is certainly the most discussed among those who held the presidency of our Society. As a fascist, he attached to psychiatry, as all medicine, a primarily political function within Mussolini's organic conception of the State. Influenced by the rhetoric of the regime, he was a supporter of the work of craftsman as typically Italian, and more physiological and healthy than the industrial one. When in 1932 Luigi Scabia (1868–1934), director of the asy-

FIGURE 4.
Enrico Morselli.

lum of Volterra [20], turned to the SIP for help against the harassment to which he was subjected because he was antifascist, his request fell on deaf ears. In the mid-1930s Donaggio joined the fascist racism ideology in terms of exaltation of the Italian race, heir to the imperial function of Rome, but in his writings a disparaging attitude towards people of colour or Jews is absent. However, he did write in a magazine which supported fierce racist and anti-Semitic positions, "La difesa della razza" ("The defence of race") [21]. In July 1938, his name appeared among the signatories of the "Manifesto of Racist Scientists", and SIP was the only scientific society to support it. At the XXII Congress of 1940, Donaggio did not deny authorship of the Manifesto, but he said that he was honoured that Mussolini had affixed his name under Mussolini's ideas, leaving it somehow understood that he was not really one of the authors, but avoiding explicit abjuration. At the end of the Proceedings of the Congress, it was announced emphatically and with enthusiasm that Italy had entered the war few days later. Donaggio was not a fierce racist; he probably adhered to the Fascist movement for vainglory, nationalist pride and perhaps convenience, in addition to opportunism, to defend his position of prestige and benefits, and perhaps that of the psychiatrists who he believed he so well represented. But it was more an opportunistic attitude of many, rather than the fanaticism of a few, that allowed the fascists to govern Italy and cause so many disasters [22].

The "Manifesto of Racist Scientists" was the scientific basis for the "Racial Laws" enacted the next autumn: Gustavo Modena (1876–1958), being a Jew, had to give up the vice presidency of the SIP and the direction of the asylum of Ancona, and other psychiatrists, such as Marco Levi Bianchini (1875–1961) [23], were forced to give up their career and scientific activities. Donaggio died in 1942 in a car accident; Modena looked for leaders who would temporarily assume the presidency, until the war would allow a new Congress. However, no one accepted and he had to keep it for himself; thus, for three years the SIP had an acting president who was forced to leave the field of study and the SIP itself by unjust laws, to which it helped provide a pseudoscientific pretext.

Ugo Cerletti (1887-1963) [24], from the University of Rome, was, after having discovered the electroconvulsive therapy in 1938, the vice president of the SIP, but he rejected the proposal of Modena in 1942 because he was in disagreement with the regime [25]. He accepted the presidency only at the XXIII Congress of 1946, where two young psychiatrists, Giorgio Padovani and Luigi Bonfiglioli, proposed a report instigated by the SIP about what happened to Italian psychiatry during the war: four psychiatrists died because of bombing or struggles in psychiatric hospitals, including Arrigo Tamburini (1878–1943), Augusto's son, in Ancona; Giovanni Mercurio (1916–1945) was captured as a partisan and died in Mauthausen; Giuseppe Muggia (1877–1944) and Guglielmo Lippi Francesconi (1899–1944) were killed by the Nazis. Many others were deported to Germany. Partisans, deserters and Jews were hidden in many psychiatric hospitals, but some Jewish patients were captured in them in north-eastern Italy by the Germans or fascist policemen, and died in lagers. Deaths in psychiatric hospitals directly due to war actions numbered about 300 among patients and staff, but other deaths between patients due to scarcity of food and drugs, and to the improvidence of authorities, ranged from 24,000 to 30,000 [26].

In 1946, Cerletti was the first to compare the Italian asylums to the Nazi concentration camps, an expression which would be used repeatedly by others in subsequent years [27]. He was president of the SIP until 1963, when he was succeeded by Mario Gozzano (1898–1996) from the University of Rome until the XXX Congress held in Milan in 1968, and then by Carlo Lorenzo Cazzullo (1915–2010), from the University of Milan, who during his youth belonged to the Resistance [28]. The same year, the SIP remained close to the Minister of Health Luigi Mariotti (1912–2004), who promoted a reform of psychiatric assistance, Law 431, with the aim of bringing it in step with the French one. The experience of Franco Basaglia (1924–1980) [29] in Gorizia was now, however, already widely advanced and in the same year his most famous book, "L'istituzione negata" (The institution denied), was published. Therefore, Law 431 was already behind the times when it was instituted. During the 1968 Congress held in Milan, Basaglia asked the SIP to support the struggle against the psychiatric hospital. However, the leadership of the SIP considered his approach too theoretically abstract and adventurous, and as being too close to the highly contesting political movements of those years. The movement led by Basaglia reproached the leadership of the SIP, formed by the most powerful psychiatrists of the University and psychiatric hospitals, to be an expression of the repressive function of psychiatry and above all to have responsibility for the dramatic condition of inmates. The first aim of Basaglia and his followers was the closure of the psychiatric hospital, while that of the SIP was to put psychiatry within a

Presidents of the Italian Society of Psychiatry 1873-2013

1873-1891 Andrea Verga (Milan)

1891-1896 Serafino Biffi (Milan)

1896-1919 Augusto Tamburini (Reggio Emilia and Modena until 1906, then Rome)

1919-1929 Enrico Morselli (Genoa)

1929-1942 Arturo Donaggio (Modena)

1942-1946 Gustavo Modena (Ancona) (de facto)

1946-1963 Ugo Cerletti (Rome)

1963-1968 Mario Gozzano (Rome)

1968-1975 Carlo Lorenzo Cazzullo (Milan)

1976-1980 Antonio Balestrieri (Verona)

1980-1982 Franco Rinaldi (Naples)

1982-1991 Carlo Lorenzo Cazzullo (Milan)

1991-1994 Dargut Kemali (Naples) - Pier Luigi Scapicchio (Rome)

1994-2000 Gaspare Vella (Rome) - Pier Luigi Scapicchio (Rome)

2000-2003 Mario Maj (Naples) - Carmine Munizza (Turin)

2003-2006 Eugenio Aguglia (Catania) - Carmine Munizza (Turin)

2006-2009 Alberto Siracusano (Rome) - Mariano Bassi (Bologna)

2009-2012 Eugenio Aguglia (Catania) - Luigi Ferrannini (Genoa)

2012-2015 Emilio Sacchetti (Brescia) - Claudio Mencacci (Milan)

medical context. The premises for an alliance were not good, and in those years of open dialectic the 1968, 1975 and 1977 SIP Congresses were troubled by heterogeneous contestation. Nonetheless, Law 180, which was passed in May 1978 when Antonio Balestrieri from the University of Verona was president, satisfied both expectations, also because soon after Law 833 on healthcare reform included it and ended the separation of psychiatric assistance from general healthcare. The favourable position towards closure of psychiatric hospitals adopted by the SIP, at least since the middle of 1970s, played an important role in convincing those who were reluctant to adopt this original and unexplored solution.

Two years before, with Law 238 of 1976, Cazzullo had obtained University Chairs of Psychiatry independents from those of Neurology, thus breaking the position of subordination which had lasted since the beginning of the century [30]. Balestrieri led the SIP from 1976 to 1980, when he was succeeded by Franco Rinaldi, from the University of Naples, from 1980 to 1982, when Cazzullo returned to its presidency until 1991. The office was then passed to Dargut Kemali (1922–2011), from the University of Naples, and Pier Luigi Scapicchio, a psychiatrist in Rome; he was the first psychiatrist who was not affiliated with a University since 1906, when Tamburini left the asylum. Times had changed after Law 180, and an amendment to the Statute established an alternation of the presidency between members affiliated with and not affiliated with a University during the triennial period between congresses.

Acknowledgements

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RESEARCH IN PSYCHIATRY: ONGOING DEBATE AND EVOLVING PRIORITIES

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The current status of research in psychiatry is less gloomy than implied by some recent reviews and commentaries. If psychiatric research seems to lag somewhat behind compared to other medical disciplines, the main reason is that the complexity of mental disorders has no equal in medicine and requires an equally complex multidisciplinary effort. However, it is probably true that we need some reconsideration and rebalancing of the priorities of psychiatric research, and it is certainly true that the viewpoint of the various stakeholders involved in the field, and in particular of users, has to be taken into account in this respect.

The notion that psychiatric research is in a crisis or in a stalemate has recently become a sort of cliché. Several very visible reviews and commentaries have asserted: a) that the diagnoses used as inclusion criteria in psychiatric research are invalid (e.g., [1]); b) that psychiatric research, in particular biological psychiatric research, has not been able to "determine what causes schizophrenia, depressive disorder or anxiety diseases", despite many decades of efforts [2]; and c) that the research documentation of the impact of psychiatric treatments is questionable (e.g. [3]). This climate of disillusionment and skepticism has generated a revival of the ideological split within our profession between those who believe that mental disorders are brain diseases and that psychiatry, as a clinical neuroscience discipline, "needs to invest greater scientific effort into studies of the etiology and pathophysiology of these major brain disorders" [4], and those who maintain that biological research "has failed to deliver anything of value to clinical psychiatrists and is very unlikely to do so in the future" [5].

These two opposite positions are now being increasingly stretched to the extreme, with the claim on the one hand that "it is time to end the distinction between mental and neurological illnesses" and that "psychiatric disorders should be reclassified as disorders of the (central) nervous system" [6], and on the other that it is the "technological paradigm" which has failed, since the balance of evidence does not support the idea that "mental health problems are best grasped through a technical idiom" (i.e., through psychiatric diagnoses) and that "good mental health work can be characterized as a series of discrete interventions" (i.e., specific pharmacological or psychotherapeutic treatments) [7].

Needless to say, these extreme positions actually converge in reinforcing the public perception that psychiatry lacks a coherent theoretical basis and that the credibility of whatever psychiatric research produces is at least doubtful.

What should our position be, as individual professionals and as psychiatric organizations, in this debate? A first point which in my opinion needs to be made is that the gloomy picture that both parties are presenting of the current status of psychiatric research is incorrect and based on simplistic assumptions and expectations. What do they mean when they state that psychiatry has not been able to determine "what causes schizophrenia, depressive disorder or anxiety diseases"? Are these people aware that the nature of mental disorders "does not yield up to a reductionist, 'one cause' etiological model" and that "this clear picture – where all roads lead to one essentialist cause – is really an exception even in general medicine" [8]? Indeed, the etiology of the most prevalent diseases in Western countries (e.g., hypertension or asthma) is now conceptualized as complex and multidimensional. There will be

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certainly no more "spirochete-like discoveries" in psychiatry [9], while what is occurring and is going to occur is the gradual elucidation of a multiplicity of risk and protective factors, which exert small to moderate effects at different levels and interact with each other in complex ways.

Using this key, one can appreciate that psychiatric research has made significant advances in the past few decades. Within a project funded by the European Commission, whose acronym is ROAMER, aiming to build up a roadmap for mental health research in Europe [10], a group of scientists has been recently asked to identify the main advances in psychiatric research during the last ten years. Well, the top two advances in the list have been "the increased understanding of gene-environment interaction as well as epigenetic mechanisms in psychiatry" and "the acknowledgement of effects of early (prenatal, perinatal, postnatal) environmental exposure and the increased understanding of the trajectory of common mental disorder along the lifespan (from childhood through adolescence into adult life)". One can easily appreciate that this research is much more complex and sophisticated, and congruent to the complexity of mental disorders, than the research that many critics of psychiatry have probably in mind, i.e., the old-fashioned comparison between a sample of patients with a given psychiatric diagnosis and a sample of healthy controls, in the search of a statistically significant difference with respect to the mean values of a given (usually biological) variable.

It can be argued that much of the above-mentioned new research has been designed and conducted not only by psychiatrists but also by other mental health and non-mental health professionals, but this is both unavoidable and welcome. Complex research requires multidisciplinary efforts, and the psychiatric profession will have an increasingly or the decreasingly prominent role in that research in the years to come as a function of its ability to realize what is now the direction of progress.

One could also argue that, in these new studies, the impact of several environmental and genetic risk factors has been found to display a substantial non-specificity for a range of mental disorders. But this should be regarded as an important research finding in itself, whose emergence has not been obstructed by the use of our current diagnostic systems. These systems, in spite of their limitations, have important merits, including the fact that they allow researchers to understand each other when they talk about a given mental disorder and to compare their findings. The existence of these systems does not prevent the emergence of other, new patterns of classification of mental disorder, based on neurobiological or behavioural or other elements, and these alternative patterns can certainly be used, and several of them have already been used, as independent variables in psychiatric research.

So, the status of etiopathogenetic research in psychiatry is less bleak than the above-mentioned reviews and commentaries imply, and our current diagnostic systems have not been an insurmountable obstacle to the progress of that research.

Coming to psychiatric treatments, is the currently emerging skepticism about their scientific foundation really justified? Well, I think that a major contribution in this respect has been provided by a recent review of meta-analyses comparing the efficacy of psychiatric vs. general medicine medications [11]. This review found that, for instance, the efficacy of antipsychotic drugs in the acute treatment of schizophrenia, evaluated in terms of standardized mean difference from placebo, is comparable to that of anti-hypertensive drugs in the acute treatment of hypertension, and is five times greater than that of thrombolytic medication in the acute treatment of stroke. Even more strikingly, the efficacy of antipsychotics in the maintenance treatment of schizophrenia is almost six times greater than that of angiotensin-converting enzyme (ACE) inhibitors in the long-term treatment of hypertension. The efficacy of antidepressants in the maintenance treatment of major depressive disorder is six times higher than that of ACE inhibitors in the long-term treatment of chronic heart failure, and the maintenance treatment of bipolar disorder with lithium is no. 3 in terms of efficacy among all treatments considered, being more effective than the long-term treatment of diabetes with metformin or asthma with corticosteroids.

These are the hard data. One could argue that the effectiveness of psychiatric medications in ordinary practice is lower than their efficacy as emerging in controlled trials, due to the poor adherence of patients to medical prescriptions and of psychiatrists to treatment guidelines. However, this is to some extent true also for medications used by other medical specialties. Furthermore, it is certainly not only our responsibility if the social context in which psychotropic drugs are used is marked by so much ignorance and ideological prejudice, thus inducing many patients and families to believe that these medications do not work and consequently to stop treatment or not to follow the prescription appropriately, and leading several psychiatrists to believe that it is not so important for

them to learn to use these drugs appropriately, since they represent only a marginal ingredient of care.
One could also argue that several psychiatric medications have significant side effects, but, again, this is true for many efficacious compounds used in medicine, and treatment guidelines are now available to prevent and address those side effects. Again, it is not only our responsibility if the use of these guidelines in ordinary practice is often not considered or even actively ostracized.
It could be further argued that the evidence of the efficacy of psychotropic drugs may have been biased by the financial conflicts of interests of investigators. However, again, this may be true also for the drugs used by other medical specialties. Moreover, it would be hard to maintain that financial conflicts of interests have had a significant impact on the evidence concerning the efficacy of lithium, a medication which has no support by the industry and has been found to be no. 3 in terms of efficacy among all drugs considered in the above-mentioned review. It could also be added that the role of ideological conflicts of interests of reviewers and commentators in minimizing or distorting the evidence of the efficacy of psychotropic drugs has no equal in the field of medicine, and that the impact of these ideological conflicts of interests on the public perception of the efficacy of psychotropic drugs is being at least as substantial as that of financial conflicts of interests [12].
So, the gloomy picture of the status of psychiatric research depicted in some recent literature is not correct. However, it is probably true that we need some reconsideration and rebalancing of the priorities of psychiatric research, and it is certainly true that the viewpoint of the various stakeholders involved in the field, and in particular of users, has to be taken into account in this respect.
Indeed, it has been pointed out that, in the field of health care in general, research agendas should reflect the needs and values of the people who use and pay for services, and that this is unlikely to be achieved without directly involving some of these people in research planning [13]. This argument is particularly relevant in the mental health field, since different stakeholders involved in this field may have different views about the desirability of various outcomes, with clinicians “typically affording pride of place to symptom reduction”, while the primary interest of families “is in receiving information, support and services” and people with mental health problems “are most concerned with issues of choice and control and the importance of decent lives” [14].

Within the above-mentioned ROAMER project, we conducted a survey among various categories of stakeholders about the priorities for mental health research in Europe [15]. The survey was carried out with the national associations of psychiatrists, psychologists and other mental health professionals, the national organizations of users and carers, and the national organizations of psychiatric trainees of the 27 countries of the European Union. A very simple online questionnaire was used, asking the respondents to select the top five priorities for mental health research in Europe from a list of research areas, with the option to identify further areas if needed, and to rate the importance and the level of development in their country of each of those research areas.
Both associations of psychiatrists and organizations of users and carers identified research on the quality of mental health services as the top one priority. The other four top priorities were different for those two groups of respondents, with psychiatrists highlighting research on early detection and management of mental disorders, new medications for mental disorders, ways to increase access to available treatments, and prevention of mental disorders, whereas users and carers laid emphasis on research on new psychological interventions for mental disorders, stigma and discrimination, rehabilitation and social inclusion, and health and well-being of carers [15]. These results seem to support the recently expressed view that some rebalancing of psychiatric research may be needed in favor of health service, social and community studies [2].
A further activity within the ROAMER project has been a series of meetings of representatives of European organizations of the various categories of stakeholders, aiming to collect their recommendations about how to increase the quality and impact of mental health research in Europe.
In these meetings, the stakeholders first of all pointed out that we need more collaboration in mental health research (more formal networks, including as many countries as possible; more multidisciplinary studies, especially in emerging integrative areas such as social neurosciences; sharing of databases of large studies after they are completed). A second recommendation was to more systematically involve users, from the very beginning, when research is planned. There are in fact already several successful experiences of participatory research in Europe [16]. A third recommendation, very much in line with one of the advances highlighted by the above-mentioned group of scientists, has been to integrate research through

the lifespan, giving priority to longitudinal cohort studies. It has been also argued that the evaluation of treatments, especially in the areas of psychotherapies and psychosocial interventions, needs to be better standardized, and that further research is needed about the active components of those interventions. It has been further noticed that we need to better explore and highlight the economic and societal impact of mental health and well-being and to conduct more systematic research on vulnerable groups, such as unemployed people, migrants, those living in poverty and people with handicap.

All these recommendations are clearly of great utility, but several of them raise a further issue: should psychiatric research focus on proper mental disorders, or should it also address the wide range of mental health problems which increasingly come to the attention of mental health services in the community [17]? There are at present different views about this issue. Some commentators (e.g. [18]) have recently echoed the old complaint by F. Redlich [19] that "psychiatry abandoned the island of psychiatric disease and was thus engulfed in the boundless sea of human troubles". However, there are areas, such as research on the precursors and prodromes of mental disorders and on the psychiatric consequences of natural disasters or of the ongoing economic crisis, in which a deeper knowledge of the ordinary, physiological responses to major stressors and life-cycle transitions is clearly necessary.

Psychiatrists need to collaborate with other mental health professionals and other relevant stakeholders in the characterization of these ordinary responses as well as of those more serious responses to the above stressors and transitions which are likely to come to the attention of mental health services although not being proper mental disorders [17]. It is useful to point out, in this respect, that the complete denomination of the ICD is "International Classification of Diseases and Related Health Problems", obviously including also mental health problems, and that both the ICD and the DSM already include chapters on "other conditions which can be a focus of clinical attention", although those chapters are at the moment somewhat elusive and of doubtful clinical relevance.

This broader focus on mental health problems which are not proper mental disorders could guide the development of cost-effective interventions and community resources for these problems. Currently, in fact, there is on the one hand the risk of an inappropriate extension of interventions used for proper mental disorders to the new emerging conditions (for instance, use of antidepressants for the understandable psychological consequences of the ongoing economic crisis), and on the other the risk to reduce the intervention to practical advice also in cases in which a professional management is needed. This research could also contribute to a clearer definition of the limits of the scope of mental health services, especially in the presence of substantially reduced resources [17].

Further recommendations to improve the quality and impact of psychiatric research have been provided within the ROAMER project [10]. One set of recommendations focused on training for psychiatric research. It was observed that there are at present no European curricula in mental health research training, that high-class senior researchers are often disincentivized out of the research system and leave it for private practice or other sectors, so that there is a lack of mentors. Problems in recruiting young people in psychiatric research were also pointed out. Another set of comments was about the persisting underfunding of mental health research as compared to the magnitude of the social burden related to mental disorders. There is a need to highlight the economic and societal impact of mental health, and to speak to governments and international organizations with a common language ("ask three psychiatrists and you get four answers": this is a common complaint by politicians and administrators and an excuse for not investing in mental health research). It was also argued that there is often a split in psychiatry between research units and technical facilities (they are too "independent" from each other), and not enough collaboration and sharing of resources (including protocols and databases) among research units. The need to massively invest in e-health and m-health approaches was also highlighted, and this is going to be endorsed in a major European project.

The promises and limitations of the Research Domain Criteria project, launched by the National Institute of Mental Health (NIMH) in the US with the aim to generate a diagnostic system based upon neuroscience and behavioural science rather than descriptive phenomenology [20], were also discussed. This project is more likely to develop neurobiological measures which help in subtyping rather than in replacing current diagnostic entities, in order to improve prediction of outcome and treatment response [21]. So, RDoC supporters should refrain from a polemic confrontation with the DSM and the ICD (e.g. [1]) which is unwarranted, disruptive to the field and confusing to patients and families and to the public opinion.

Furthermore, the gap between RDoC constructs and

the clinical phenomena we observe in clinical practice remains wide, especially in some areas such as that of psychoses. I recently chaired a meeting with the participation of the NIMH and the World Health Organization leadership, in which possible ways by which we clinicians can contribute to reduce this gap were considered, including a redefinition and dissection of complex symptoms (e.g., delusions), the search for experiential as opposed to behavioral intermediate phenotypes (e.g., the primary pathological experiences underlying delusions in schizophrenia), the refinement of currently identified dimensions of some mental disorders, a more precise characterization of some broader dimensional groupings or spectra (e.g., internalizing/externalizing disorders) and a refinement of the staging recently proposed for some mental disorders. Developing cross-walks between the RDoC and the current diagnostic systems, in a climate of reciprocal respect, is an endeavour that can only enrich psychiatry and related disciplines [21].

In conclusion, the current status of research in psychiatry is less gloomy than implied by several recent reviews and commentaries. If this research seems to lag somewhat behind compared to other medical disciplines, the main reason is that the complexity of mental disorders has no equal in medicine and requires an equally complex multidisciplinary effort. It is to be hoped that the ongoing debate will lead to an intensification and a further articulation and qualitative improvement of this effort, rather than resulting in a widespread demotivation or a revival of outdated polarizations.

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PREVENTING VIOLENCE IN SCHIZOPHRENIA

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Abstract

Background. High rates of violence have been reported in clinical samples of patients with schizophrenia, especially of first episode psychosis, and there is an over-representation of people with schizophrenia among samples of violent offenders.

Method. A review of case linkage studies, studies of violence and stage of illness, studies of factors associated with violence in schizophrenia, and outcome studies, to identify strategies that might reduce the incidence of violence by people with schizophrenia.

Results. Case linkage studies show a peak in violent offending in the period before the diagnosis of schizophrenia. Studies of stage of illness and violence show that a large proportion of serious violence is committed prior to initial treatment for schizophrenia, often after long period of untreated psychosis. The main factors associated with violence in schizophrenia are comorbid substance abuse and delusional beliefs in which the patient believes they are in danger or have been seriously wronged. Outcome studies suggest that long term supervision of treatment after committing an act of violence reduces the incidence of further violent offences. There were no studies showing that the routine use of any form of risk assessment was able to reduce rates of violence among people with schizophrenia.

Conclusions. Interventions that might reduce the incidence of violence in schizophrenia include earlier and adequate treatment of the first episode of psychosis, improvement in methods of treating substance abuse in people with schizophrenia, including involuntary treatment for those who have committed offences associated with intoxication, assertive treatment of patients with alarming symptoms, and long term supervision of patients who have committed serious violent offences. The low base rates of serious violence and the absence of specific risk factors that might predict which patients might commit an act of violence means that the best way to reduce violence is not by attempting to predict which patients might commit an act of violence, and is instead by reducing barriers to care and by systems of care for the continued treatment for all patients, especially those with a history of violence

Key words: Violence, prevention, schizophrenia, first episode, substance use, risk assessment

Introduction

Most people diagnosed with schizophrenia will never commit an act of serious violence. However, people with schizophrenia are over-represented among samples of serious violent offenders, as although they comprise about 0.44% of the population [1], they make up about 6.5% homicide offenders [2], and around 10% of offenders charged with serious non-lethal violence such as assault causing significant harm and wounding [3]. People diagnosed with schizophrenia are also over-represented in prison populations, with the proportion of samples of prisoners being diagnosed with schizophrenia ranging from 5% to 10% [4,5]. Hence

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there is no escaping the fact that a disproportionate amount of serious violence is committed by people with schizophrenia, and violence prevention strategies should consider how best to reduce violence by the mentally ill.

Stage of illness and violence

In recent years there has been an increasing interest in the phase of illness in which violent offending is likely to occur. Three studies linking criminal histories to medical records have shown a peak in conviction for violent offences in the years prior to diagnosis [6-8], and in the case of the study from Denmark, nearly 75% of violent offences by the mentally ill were committed in the four years prior to initial treatment [6]. There have been similar findings for homicide. A meta-analysis of ten published studies of homicide in psychosis in which a treatment history was reported showed that 39% of psychotic homicide offenders had never been treated, suggesting a fifteen fold increase in the risk of homicide prior to treatment [9]. These studies confirm that the first episode of mental illness, and the period immediately prior to diagnosis and the initiation of treatment, is the period of greatest risk for violence.

The relationship between violence in schizophrenia and all violence

It was previously believed that homicide by people with schizophrenia was related to the epidemiology of the disorder and was unrelated to the total homicide rate. However, a recent meta-analysis has demonstrated that in fact, the rates of homicide by people with schizophrenia is strongly correlated with the overall rate of homicide [2], including in regions with very high rates of homicide [10]. However, the rate of homicide by people with schizophrenia was found to be about ten times higher than the rate for the general population, regardless of the total homicide rate, indicating that people with schizophrenia are especially vulnerable to the sociological factors that influence the total rate of homicide and serious violence in the community.

There are a number of possible explanations for this finding. The first is that although a proportion of homicide offences are committed in response to frightening symptoms of mental illness, which might not have occurred had the person received effective treatment, the presence of a high rate of violence in a community might also indicate less effective systems for treating people with severe mental illness. The second possible explanation is that people with schizophrenia, which is after all a disorder affecting the function of the frontal lobes of the brain, are particularly prone to substance use and more sensitive to patterns of substance use associated with violence, especially alcohol, cannabis and stimulant drugs. A third explanation is that the social conditions that produce a high rate of violence have a particularly severe effect on people with mental illness, who are often victims of violence[11] and who are more likely to live in more crowded and violent neighbourhoods because of the poverty and social disability associated with mental illness.

What makes people with schizophrenia violent?

Many studies have examined the factors associated with violence in schizophrenia. Studies based on the outcome of court cases have tended to concentrate on the pattern of acute symptoms that were present at the time of the violent act. For example, in one series of cases in which the inclusion criteria was the availability of the defence of mental illness, 96% of the subjects were reported to be motivated by a delusional belief, usually the belief that the victim posed a serious threat to the offender [12]. Other types of delusions associated with violence include the delusion that the victim had committed a terrible wrong, delusions of jealousy, and misidentification delusions, for example, Capgras delusions [13].

However, recent reviews examining the diagnosis and offences, including offences committed throughout the course of illness, have noted the relationship between substance use, violence and the diagnosis of schizophrenia, even in people with the diagnosis who are receiving treatment and are generally free of acute symptoms [14,15]. Substance use in particular is known to trigger symptoms, is associated with poor adherence to treatment [16] and may have a disinhibiting effect in people who already have impairment in frontal lobe function.

Can treatment reduce the incidence of violence?

While there is no direct evidence from controlled trials that treatment reduces the incidence of violence, there is evidence that earlier treatment of first episode might reduce the incidence of major and minor violence [17], and both serious [18] and less serious

forms of self harm [19]. The proportion of homicides committed prior to treatment is directly correlated with the duration of untreated psychosis [20]. About 16% of all patients have committed an act of actual physical violence prior to initial treatment [17], 18% have self harmed [19], and as many as half of the survivors of violent suicide attempts have been found to have an untreated psychotic illness [18]. A public health initiative in Norway designed to reduce the duration of untreated psychosis has had a measurable effect on the incidence of self harm [21].

There is also some evidence that continued adherence to treatment can reduce the incidence of violence by people with schizophrenia. A study of serious non-lethal violence in psychotic illness found that of the 80% of offenders who were known to services, only 16% were currently receiving treatment [3]. However, the rate of re-offending by conditionally released forensic patients in New South Wales, Australia, nearly half of whom had committed homicide offences, was negligible, mainly because of the careful supervision of adherence to treatment [22]. Very low rates of homicide recidivism have been observed in most other jurisdictions with comprehensive community forensic services [23]. By contrast, the rate of homicide recidivism in the Chuvash republic of the Russian Federation was nearly 10%, and nearly all recidivist homicides occurred in rural areas, where there was little in the way of services [24].

Can risk assessment assist us to reduce violence by people with schizophrenia?

Risk assessment will be of little or no value in identifying patients with schizophrenia who will go on to commit an act of serious violence (or commit suicide, for that matter) because the base rate of serious violence is too low, and the factors shown to be associated with violence are too common to discriminate high risk from low risk patients in a meaningful way [25]. An example of the absurdity of risk assessment can be seen in the introduction of a requirement for a pre-discharge risk assessment for all patients, in the aftermath of an enquiry about the homicide of a stranger by a recently released psychiatric patient in the UK. The base rate of stranger homicide is about 1 in 140,000 patients with schizophrenia per annum [25], and even if it were possible to detain 30,000 patients for a year in order to prevent one homicide of a stranger, we would still miss the two thirds of such cases that are committed by mentally ill offenders who have not yet received treatment and are not known to services [26].

How should we treat substance use in psychosis?

Current treatment guidelines in several countries recommend motivational interviewing, a technique drawing from cognitive behavioural principles to assist patients identify their patterns of substance use and devise their own treatment plans [27]. However, apart from several studies of “integrated therapy”, which combines counselling and environmental interventions [28], there is surprisingly little evidence for the efficacy of any form of psychosocial intervention for comorbid substance use in psychosis [29]. One reason for the poor results could be that nearly all studies are dealing with patients with more entrenched substance use, as about 50% of cannabis users give up cannabis in response to medical advice alone after the first episode of mental illness [30]. There is also some evidence that conditional release is a strong incentive for abstinence from substance use, and continued monitoring for drug use may also reduce the incidence of substance use after offences [22].

How then can we reduce violence by people with schizophrenia?

Firstly, we need to reduce the duration of untreated psychosis (DUP). Research has shown that mean DUP is six months shorter in regions with “need for treatment” mental health laws, rather than the requirement that the patient has to be shown to be dangerous to self or to others before they can receive involuntary treatment [31]. Reducing other barriers to diagnosis and treatment, including the awareness of the harms associated with untreated psychosis, and re-engineering first episode services to actively seek cases, rather than passively wait for referrals, could also reduce DUP [32]. Raising public awareness of early psychosis has also helped reduce DUP [21].

The other main intervention that would be likely to reduce the incidence of violence would be any measure that ensures continuity of care, especially the care of people with a history of violence. A striking feature of many services is the poor use of data, including internal audits of treatment, and the way in which the mobility of patients results in loss of continuity of care. Measures that might improve care, especially for those with a history of violence, might be to link treatment to social security payments, and the use of forensic type conditional release orders to

ensure adherence to treatment and abstinence from substances associated with violence.

A further consideration is the effect of violence in the wider community. Any measure that reduces violence, for example, better policing, better design of public housing and reduced availability of alcohol, is likely to have a far greater effect on violence by the mentally ill.

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SUICIDAL BEHAVIOUR IN PATIENTS WITH MOOD DISORDERS

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Abstract

The risk of suicidal behaviour in mood disorders is an inherent phenomenon and in patients with major mood disorders it strongly relates to the presence and severity of depressive episode. Suicidal behaviour in patients with mood disorders is state and severity dependent that means that suicidality markedly decreases or vanishes after clinical recovery. However, since the majority of mood disorder patients never commit and more than half of them never attempt suicide, special clinical characteristics of the illness as well as some personality, familial and psycho-social factors should also play a contributory role. Considering the clinically explorable suicide risk factors in patients with major mood disorders (family and/or personal hisotry of suicidal behaviour, early onset of mood disorder, severe depressive episode/hopelessness, agitated/mixed depression, bipolar I or II diagnosis, rapid cycling course, comorbid Axis I and Axis II disorders, adverse life situations, lack of social and medical support, cyclothymic temperament, impulsive aggressive personality features, etc.), suicidal behaviour is predictable with a good chance. Successful acute and long-term pharmacotherapy markedly reduces the risk of attempted and completed suicide, even in this high-risk population. Supplementary psychosocial interventions (psychoeducation and targeted psychotherapies) further improve the results.

Keywords: Major depressive disorder, bipolar disorders, suicidal behaviour, suicide risk factors, pharmacotherapy, psychosocial interventions

Introduction

Suicidality is one of the most alarming signs in psychiatry and it is the most hard end-point and most visible treatment outcome in patients with psychiatric disorders. Suicidal behaviour is very complex, multi-causal behaviour, involving several medical-biologic, psychosocial and cultural components, and history of untreated major mood disorders (particularly in the presence of previous suicide attempt) is the most important risk factor. However, because the majority of mood disorder patients never complete (and around 50% of them never attempt) suicide, other familial-genetic, personality, psychosocial and demographic risk factors should also play a significant contributory role [1-4].

Psychological autopsy studies from different parts of the world consistently show that around 90% of consecutive suicide victims have one or more Axis I (mostly untreated) major psychiatric disorders at the time of their death, and major mood disorders (59-87%) schizophrenia/schizoaffective disorder (10-12%) and substance-use disorders (10-15%) are the most common principal diagnoses. Comorbid anxiety and personality disorders are also frequently present, but they are rare as principal (or only) diagnoses [1 3-5]. It has been estimated that 15-19% of severe (mostly hospitalized) patients with major depression would die by suicide [6]. In their meta-analysis of studies on suicide risk in psychiatric disorders,

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Harris and Barraclough [7] analysed separately the risk of suicide in unipolar major depression and in bipolar disorder. They found that the risk of suicide was about 20-fold for patients with index diagnosis of unipolar major depression, and the same figure for bipolar disorder was 15. However, these studies [6 7] cannot provide a precise estimation of separate suicide risk in unipolar and bipolar disorder, i.e. they overestimate the risk for unipolar depression and underestimate it for bipolar disorders. The main sources of these are that the index diagnosis frequently change during the long-term course from unipolar depression to bipolar I or bipolar II disorder [8-11] and in the studies (performed several decades ago) reviewed by the mentioned authors the diagnostic category of bipolar II depression (depression with hypomania but without mania) which is quite common form of bipolar disorders [9 12] has not been considered separately and it is very likely that the majority of bipolar II patients in these studies were included in the unipolar major depressive subgroup. Indeed, a recent long-term follow-up study showed that the rate of completed suicide was about double in bipolar disorder (types I and II combined) than in unipolar depression [13]. Another three recent population based epidemiological studies also found a substantially higher rate of suicide attempts in bipolar (types I and II combined) than in unipolar major depressive disorder patients [14-16].

Risk of suicidal behavior in patients with unipolar major depression or bipolar disorders

Completed suicide

The different suicide risk in the three main subgroups of major mood disorders has been first reported by Dunner et al. [17] who found that 3% of the 73 unipolar, 6% of the 68 bipolar I and 18% of the 22 bipolar II patients died by suicide during their 1-9 year follow-up study. In contrast to this, in a 40 to 44 years' prospective follow-up study of 406 formerly hospitalised (186 unipolar and 220 bipolar) major mood disorder patients, in which the unipolar-bipolar conversion was carefully considered during the follow-up, Angst et al. [18] found that 14.5% of unipolar and 8.2% of bipolar (I + II) patients completed suicide; the SMRs for suicide in unipolar and bipolar patients were 26 and 12, respectively.

In their recent long-term prospective follow up study (average 11 years) on 1983 unipolar major depressives and 843 bipolar (I + II) patients, Tondo et al. [19] found five-times fold higher rate of completed suicide in bipolar I and II than in unipolar patients (0.25% of patients/year vs. 0.05% of patients/year). This study also found that the ratio of attempted to completed suicide in bipolar II, bipolar I and unipolar depression was 5, 11, and 10, respectively, showing that the lethality of suicide attempts was far highest in bipolar II patients. The higher risk of suicide of bipolar II than bipolar I and unipolar patients has been also supported by the study of Sani et al. [16]. During this long-term (up to 35 years) follow-up study on 4441 formerly hospitalized psychiatric patients it has been also found that bipolar II patients had the highest risk for suicide; 2.8% of 1163 bipolar I and 4.2% of 602 bipolar II patients completed suicide while the same rate of 1142 unipolar major depressive patients was 1.9% [13]. Similarly, in the STEP-BD study (4360, mostly pharmacologically treated bipolar patients; mean follow-up period was 16 months) the rate of completed suicide was more than two-fold higher in bipolar II (0.34%) than in bipolar I patients (0.14%) [20]. Investigating the risk of completed suicide in a total Danish national cohort of patients with first psychiatric discharge (n = 176.347) Nordentoft et al. [21] found that the lifetime risk for suicide in bipolar disorders were 7.8% for males and 4.8% for females, while the same figures for patients with unipolar depression were 6.7% and 3.8%, respectively.

Two psychological autopsy studies where the prevalence of bipolar II, bipolar I and unipolar depression have been analysed separately show that among the 125 consecutive suicide victims with primary major depression at the time of suicide 44% had bipolar II depression, 2% had bipolar I depression and 54% had first episode or recurrent unipolar depression [22 23]. Because the lifetime prevalence rates of DSM-III/IV-defined bipolar illness in the population are relatively low compared with unipolar major depression (2-5% and 15-17%, respectively) [24-26], these results – in agreement with other findings [13 20] – also suggest that among different subgroups of major mood disorders the bipolar – particularly bipolar II – types carry the highest risk of completed suicide.

Suicide attempts

Up to fifty percent of patients with major mood disorders have at least one suicide attempt during their lifetime [2 4 15]. Considering only the ten studies, in which unipolar, bipolar I and bipolar II patients were analysed separately, the rate of previous suicide attempts is the lowest in unipolar major depression (13 %) highest in bipolar II patients (33%), and intermediate in bipolar I patients (28%) [2]. Re-analysing the ECA database, Judd and Akiskal [27] also reported that the rate of prior suicide attempt(s) was higher in bipolar II (34%) than

in bipolar I (24%) patients, while the same figure for unipolar major depression was only 16% [28]. Similarly, a study from Norway on 201 major mood disorder patients found that the lifetime history of suicide attempts in bipolar II, bipolar I and unipolar depressives were 61%, 50%, and 30%, respectively [29].

A German ten-year prospective longitudinal study showed that 32% of 33 bipolar II, 17% of 65 bipolar I and 6% of 286 pure unipolar major depressive patients attempted suicide during the follow-up [14]. In the Finnish Jorvi Bipolar Study 16% of the 90 bipolar I and 25% of the 101 bipolar II patients have reported at least one prior suicide attempt at the index episode [30]. Similar findings were reported from South-Korea; 17% of the 71 bipolar I and 36% of the 34 bipolar II patients reported the history of suicide attempt [31]. Looking at the different diagnostic subtypes of consecutive suicide attempters with current DSM-IV major depressive episode, it has been also found that bipolar, and particularly bipolar II patients were relatively overrepresented among them both in Budapest, Hungary and in Rome, Italy [32 33].

The long-term prospective study by Tondo et al. [19] found that the annual rate of suicide attempts during the follow-up was more than double in bipolar (I + II) than in unipolar patients and it was higher in bipolar I (1.52%), than in bipolar II (0.82%) and in unipolar (0.48%) depression. In a most recent population-based study on 935 bipolar I and 494 bipolar II patients Bega et al. [34] reported that lifetime suicide attempts were more common in bipolar I patients: 29% of bipolar I and 15 % of bipolar II patients reported past suicide attempt. Similarly, in the STEP-BD study 4,6% of bipolar I and 3% of bipolar II patients have made suicide attempt during the 18 month follow-up [20].

The role of mixed (bipolar) depression in suicidal behaviour

The majority of the studies shows that officially diagnosed DSM-IV bipolar disorders carry much higher risk of suicidal behaviour than unipolar major depressive disorder indicating that the bipolar component of major mood disorders could be one of the responsible factors. Therefore it is not surprising that subthreshold intradepressive (hypo)manic symptoms during DSM-IV unipolar major depressive disorder (mixed depression) also increase the risk of suicidal behaviour. It is important to note that mixed depressive episode (depression plus 3 or more co-occurring intradepressive hypomanic symptoms) and agitated depression are greatly overlapping conditions [35 36].

Analysing the NCS-Replication database Angst et al. [15] also reported that the history of lifetime suicide attempts was the highest in bipolar I (66%), lower in bipolar II disorder (50%) and lowest in unipolar major depression without subthreshold bipolarity (30%). However, in patients with unipolar major depression with lifetime or current (intradepressive) subthreshold (hyp)omanic symptoms, the rate of patients with prior suicide attempt was intermediate between pure unipolar major depression and bipolar II disorder (41%). Similar findings have been reported by Jabben et al. [37]: the lifetime history of suicide attempts in bipolar I, bipolar II and unipolar depression were 37%, 21%, and 18%, respectively, but the same rate in unipolar major depressives with subthreshold hypomanic symptoms was 38%. The importance of subthreshold bipolarity in patients with major depressive episode in suicidal behaviour is further underscored by the findings that those bipolar I or II depressives with some clinically significant intradepressive (hypo)manic symptoms showed significantly more suicide attempts at the index episode and during the long-term follow-up (54% and 58%, respectively) than those with no clinically significant (hypo)manic symptoms (32% and 35%, respectively) [38]. Investigating 87 young adults with DSM-IV diagnosed major depressive episode it was also found that 36% of bipolar depressives (types I and II combined) and 15% of pure unipolar depressives have made at least one prior suicide attempt, and the same rate in unipolar depressive patients with subthreshold (hypo)manic symptoms was 25% [39]. The elevated risk of suicidality in bipolar and bipolar spectrum patients could be the result of a complex interaction of several clinical factors, as threshold and subthreshold bipolar patients are most often mixed/agitated, show frequently rapid cycling course, predominant depressive polarity and they show a higher rate of anxiety and substance-use comorbidity.

Clinically detectable suicide risk factors in patients with major mood disorders

Specific clinical and personality characteristics

Major mood disorder patients with early onset of the illness, hopelessness, insomnia as well as with comorbid anxiety, substance-use and personality disorders are also at an increased risk of attempted or completed suicide [2-4 28 32 40-43]. Beside the highest lethality of suicide attempts [13 19], the major causes of the highest suicide risk in bipolar patients may be the high rate of comorbid anxiety disorders [42 44], substance-use disorders [4 45] and depressive mixed states/agitated depression [9 13 36 38 46-48].

Impulsivity as a personality trait increase suicide risk when combined with depression and even modest manic symptoms during bipolar depressive episodes are associated with greater level of impulsivity and higher rate of suicide attempts [49-51]. Current findings also show that in contrast to hyperthymic temperament cyclothymic/irritable/depressive affective temperaments, that are characteristic also for bipolar (mainly for bipolar II) disorder also increase the risk of suicidal behaviour in patients with bipolar and unipolar major depressive episode [52-54].

Personal and family history of suicide

Family history of suicide among first and second degree relatives [17 55 56] and past suicide attempt(s) [2 3-5 57] have been also shown as powerful risk factors for attempted or completed suicide, particularly during major depressive, mixed depressive or dysphoric manic episodes. Bipolar and unipolar patients with family history of suicidal behavior and exposed to childhood physical and/or sexual abuse are at greater risk for suicide attempts [51 57]. Impulsivity seems to be the link between childhood abuse and suicidal behavior particularly in the case of major depressive episode [58]. A study on 211 patients suffering from recurrent unipolar major depression or bipolar (I-II) disorder, hospitalized after suicide attempt, it was found that family history of suicide was significantly associated with the diagnosis of bipolar disorder and looking for the features associated with serious suicide attempt, bipolar disorder was the only associated diagnosis [59].

Adverse life events

Adverse life events play important role in suicidal process as predisposing (childhood events, including physical and sexual abuse) and precipitating (adulthood events) factors [51]. Although negative life events do not lead inevitably to suicidal behavior in healthy persons or even in the high-risk groups such as psychiatric (particularly mood disorder) patients, but they may actually trigger the suicidal process [1 60 61]. Over 40 percent of patients with bipolar disorder report a history of childhood physical and/or sexual abuse and depressed patients with such a history have earlier age of onset of bipolar illness, greater psychiatric comorbidity and increased rates of suicide attempts [43 57]. About half of all completed suicides in both bipolar I and unipolar mood disorders are associated with recent negative life events, but the stressors are commonly dependent on the victims's own behaviour, particularly in the case of bipolar I disorder [60]. Hypomanic and particularly manic episodes can easily lead to aggressive-impulsive behavior, financial extravagance, or episodic promiscuity, thus generating several interpersonal conflicts, marital breakdown and new negative life events, all of which have a negative impact on the further course of the illness which may ultimately trigger suicidal behavior. Permanent adverse life situations (e.g., unemployment, social isolation) as well as acute psychosocial stressors (e.g., loss events, financial breakdowns) in adult patients with unipolar or bipolar disorders are useful indicators of suicidality in the clinical practice, primarily if other risk factors are also present [60-63]. In the majority of cases more than one suicide risk factor are present simultaneously and their effect is cumulative: the higher is the number of risk factors the higher is the suicide risk [2-4 64]. More than one-third of suicide victims have made at least one prior suicide attempt which indicates that the majority of suicide victims die by their first attempt [1 3] and since most of them have a (mainly untreated) current major depressive episode, it is very important to detect suicide risk as early as possible, particularly in depressed patients, and intervene even prior to the subject making his/her first suicide act.

Suicide protective factors in major mood disorder

In contrast to numerous suicide risk factors, only a few circumstances are known to have a protective effect. Good family and social support, pregnancy and postpartum period, having a great number of children, holding strong religious beliefs, and restricting lethal suicide methods (e.g., to reduce domestic and car exhaust gas toxicity and to introduce stricter laws on gun control) whenever possible, seem to have some protective effect [65-67]. Recent studies have found that hyperthymic temperament may be also a protective factor [52 53 68 69]. However, one of the most extensively studied and changeable suicide protective factor in major mood disorders is the acute and long-term pharmacological treatment [4 18 43 70 71].

Medical contact before suicidal events

Despite of the fact that up to 66% of suicide victims contact different levels of health care (mostly GPs and psychiatrists) during the 4-week period before their suicide, the rate of adequate pharmacotherapy among depressed suicide victims is disturbingly low [1 22 72 73]. While the current prevalence of DSM-III/DSM-IV or ICD-10 major depression in the primary care practice is around 8-10%, the majority of depressed patients

are not recognised by their GPs. Moreover, the rate of adequate antidepressive pharmacotherapy among diagnosed depressives was less than 20%. However, studies performed 5-10 years later, reported much higher rates of recognition and treatment of depression in primary care practice (62-85%) and 33-50% of them were treated with antidepressants [69 74].

Since successful acute and long-term pharmacotherapy of mood disorders relieves not only the clinical symptoms, but parallel with this also decreases or vanishes suicidality, the appropriate treatment of mood disorders is a key issue in suicide prevention [3 4 23 43 69 71 72 75 76].

Table I shows the clinically most important suicide risk factors in patients with major mood disorders.

The role of underlying bipolarity in antidepressant-resistance and antidepressant-associated suicidal behaviour

One of the most common sources of antidepressant-resistance is the unrecognized bipolar nature of the "unipolar" major depressive episode [71 77-79]. Unrecognized bipolar depressives (mainly bipolar II depressives in the daily clinical practice) and mixed "unipolar" depressed patients with intradepressive (hypo) manic symptoms in the randomized controlled trials on unipolar major depression are considered as "unipolar" major depressives that means that these patients receive antidepressants and co-administered anxiolytics but not mood stabilizers [14 15]. This can result in a high rate of treatment resistance, which is about two-times higher in patient groups mentioned above compared to patients with true unipolar major depression. In open clinical studies the frequency of antidepressant-resistance ranges from 41-65% in bipolar (types I and II combined) depression and between 18-27% in unipolar depression [71 77 78]. Another study have shown that 80% of AD-resistant "unipolar" depressives have threshold or subthreshold bipolar disorder [80]. In addition, it has been found that the rate of the bipolar spectrum disorder among the 212 DSM-IV defined antidepressant responsive unipolar major depressive disorder inpatients was 3.8% but the same figure in 68 antidepressant-resistant inpatients was 47.1% indicating that the underlying bipolar diathesis was important contributor to antidepressant nonresponse. Similarly, a significantly higher rate of antidepressant nonresponse in „pre-bipolar" major depressives than in pure major depressives have been also reported by Li et al. [79].

Moreover, antidepressant monotherapy – without the coadministration of mood stabilizers or atypical antipsychotics – in bipolar and bipolar spectrum depressive subjects can worsen the cross-sectional picture of depression (particularly in adolescents and young adults) not only by causing (hypo)manic switch, but also via inducing or aggravating depressive mixed state/agitation, that is the major substrate of suicidal behaviour [9 47 70 71 78 81]. The retrospective chart-review of 17 patients with "pre-bipolar" major depression (i.e., patients who become bipolar I and II during the follow-up) and of another 17 patients with pure unipolar depression showed that family history of completed suicide and bipolar disorder, early onset of major depressive episode as well as treatment-emergent mixed depression, mood lability, psychomotor activation, suicidality and non-response to antidepressant monotherapy were significantly more common in "pre-bipolar" than in pure unipolar depressives [78]. Initial antidepressant monotherapy of patients subsequently diagnosed as bipolar disorder may result in higher switch rate and more frequent suicidal behaviour [81].

However, recent results show that a significant part (30-40%) of DSM-IV diagnosed unipolar major de-

Table I. Clinically detectable suicide risk factors in patients with mood disorders.

• Diagnostic subtype: Bipolar II = Bipolar I > Unipolar
• Early onset of the illness (< 25 years)
• Previous/current suicidal ideation
• Previous suicide attempt
• Current clinical features: - Severe depression, hopelessness, insomnia, guilt; - Mixed depressive episode/agitatated depression; - Dysphoric (mixed) mania or hypomania; - Mixed affective episode; - Rapid cycling course; - First episode depression, predominantly depressive polarity; - Comorbid anxiety/anxiety disorders, substance-use and personality disorders; - Cyclothymic/irritable/depressive affective temperaments; - Impulsive/aggressive personality features
• Family history of suicide in first- and second degree relatives
• History of childhood physical and/or sexual abuse
• Permanent adverse life situations, acute psychosocial stressors
• Lacking adequate acute and/or long-term treatment/care
• Noncompliance with the acute and/or long-term treatment

pressive disorder patients have clinically significant lifetime or current subthreshold (hypo)manic symptoms (mixed depression), as well as other basic clinical features (family history of bipolar disorder, early onset, bipolar conversion, etc.) that are characteristic and external validators for bipolar disorder [14 15 35 82]. This means that more than one-third of DSM-IV diagnosed unipolar depressives are in fact subthreshold bipolar depressives and beside the antidepressant resistance primarily these patients are the subjects of bipolar conversion [14 82]. The slightly elevated (but in absolute sense quite low) risk of suicidal behaviour among patients taking antidepressants compared to those taking placebo in randomised controlled antidepressant trials on DSM-IV diagnosed unipolar major depressive disorder might be the consequence of the depression-worsening potential of antidepressant monotherapy in subthreshold and mixed bipolar depressed patients who were included into these trials falsely diagnosed as suffering from unipolar depression [70 71 76]. Antidepressants can worsen depression but it is not the case for placebo and worsening of depression is the "final cause" of suicidal behaviour even in drug-free patients. In other words, when antidepressants worsen depression in a few patients, its psychopathological substrate might well reside in an agitated, excited, mentally overstimulated, anxious (bipolar) depressive mixed state [9 70 71].

Successful acute and long-term treatment of unipolar major depression and bipolar disorders markedly reduces the suicide morbidity and mortality even in this high-risk population but – as mentioned above – antidepressants can worsen depression and can lead to suicidal behavior in a small vulnerable subpopulation [18 43 70 76]. However, in the everyday clinical practice, the suicide preventive effect of antidepressants highly overshadows this unwanted iatrogeny. As the consequence of the FDA Black Box Warning (BBW) in 2004, the recently decreased use of antidepressants in children and adolescents seen in some countries has been accompanied by a concurrent increase in suicide rates in that age-groups while in middle-aged and old persons, where the utilization of antidepressants increased continuously the suicide rates decreased. These findings provided further support that the BBW, contrary to its intention, resulted in the increasing number of untreated young depressives and – ultimately – the markedly increased suicide mortality of this age group. This increase occured among young persons without antidepressant treatment [83 84]. The formal recognition of depressive mixed states in our official diagnostic system (a mixed features specifier across all mood syndromes in the DSM-V) will help to mark out those pseudo-unipolar mixed depressives for whom mood stabilizer and/or atypical antipsychotic is the appropriate treatment (at the same time antidepressant monotherapy is contraindicated for these patients).

Suicide prevention in mood disorders – Pharmacological and psychosocial treatments

As suicidal behavior in unipolar and bipolar patients occur mostly during severe pure or mixed depressive episodes and less frequently in the frame of dysphoric (mixed) mania, but practically never during euphoric mania and euthymia [2 3 43 47], it is not surprising that effective acute and long-term treatment of mood disorders have a strong protective effect against suicidal behaviour [18 76] and probably against other complications such as secondary substance-use disorders, marital instability, loss of job, cardiovascular morbidity/mortality, violent behaviour, etc.

Recently, effective psychosocial interventions in the field of mood disorders were developed primarily for patients who show insufficient response to acute and long-term pharmacotherapy, who cannot tolerate drugs or who are noncompliant with the treatment [85 86]. The interaction between pharmacotherapy and psychosocial interventions is quite complex as successful episode-preventive medication counteracts dysfunctional cognitions (including low self-esteem) and adjunctive cognitive therapy helps to optimize the long-term course [87].

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LONG-ACTING INJECTION ANTIPSYCHOTIC MEDICATIONS IN THE MANAGEMENT OF SCHIZOPHRENIA

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Abstract

Antipsychotic drugs are recommended both for the treatment of the acute episodes and the prevention of recurrence of psychosis. Long-term goals of treatment of schizophrenia include relapse prevention, recovery, improved adherence to therapy and improved patients' quality of life. Antipsychotics in combination with other therapeutic interventions are considered essential for the achievement of these long-term goals.

However, relevant issues relating to the pharmacotherapy of schizophrenia still remain unresolved. Poor adherence to antipsychotic therapy is an important factor that contributes to possible inadequacy of treatment. A considerable effort has been put into the development of antipsychotic drugs with better tolerability, or in formulations that enable less frequent administration, including long-acting injectable (LAI) antipsychotics. In recent years, the development of these formulations with atypical antipsychotics and the promising results obtained in well conducted trials with these compounds are changing the attitudes towards these drugs, traditionally reserved to patients with long-term histories of non-adherence to treatment.

The discovery and development of antipsychotic drugs more than 50 years ago has significantly improved the quality of life of patients with schizophrenia and currently there is little doubt about the substantial benefits of antipsychotics [1]. Antipsychotic drugs are generally recommended for all stages of schizophrenia, for the treatment of acute episodes of psychosis and for the prevention of recurrence [2]. Important long-term goals of current treatment for schizophrenia include relapse prevention, recovery, improved adherence to therapy and improve patients' quality of life. Antipsychotics in combination with other therapeutic interventions are considered as essential for the achievement of these long-term goals.

Several relevant issues relating to the pharmacotherapy of schizophrenia – especially when starting treatment and for how long to continue it – still remain unresolved and often result in an inadequacy of treatment for many patients, such as its premature termination or delayed access to treatment [1]. Poor adherence to antipsychotic therapy is another important factor that contributes to possible inadequacy of treatment [3]. A considerable effort has been put into the development of antipsychotic drugs with better tolerability in order to improve adherence, or in formulations that enable less frequent, and by this a more reliable administration, including long-acting injectable (LAI) antipsychotics. In recent years the development of these formulations of atypical antipsychotics and the promising results obtained in well conducted trials with these compounds are changing the attitude towards these drugs,

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traditionally reserved to patients with long-term histories of non-adherence to treatment [4].

The importance of continuity of treatment

The course of schizophrenia is characterized in about three quarters of the cases by phases of remission alternating with phases of relapse: after the first episode, it is estimated that only 14-20% of patients will recover completely [2]. In addition, knowledge about the neurobiological basis of schizophrenia has provided evidence of the often progressive nature of the disease [5]. There is clear evidence indicating that the suspension of treatment is associated with a relapse in most cases [2]. It is also increasingly evident that early intervention in psychosis may have positive effects on the long-term course of illness, while a delayed access to mental health services in recent-onset schizophrenia seems to be associated with slower or incomplete recovery, an increased risk of recurrence and an overall poor outcome [6]. Continuity of treatment already in the early stages seems crucial and may alter the outcome of the disease. A study published by Robinson et al. [7] clearly showed that despite a generally good response to initial treatment, patients with a first episode of schizophrenia had a cumulative recurrence rate greater than 80% within five years. After the initial remission, discontinuation of antipsychotic medication was identified as a significant risk factor for recurrence, resulting in an almost five times increased risk.

There is a multitude of relapse prevention studies in schizophrenia in general, but so far only a few controlled clinical trials have evaluated the possibility of preventing relapse in patients suffering specifically from a first episode of schizophrenia. In one of these studies [8], 131 first episode patients in remission for at least six months were randomized to discontinue treatment or continue it, for the most part with lower doses of atypical antipsychotics, and were followed for 18 months. Discontinuation was associated with a significantly higher recurrence rate (43% *vs*. 21%, $p < 0.011$). A more recent randomized controlled trial (RCT) [9] compared continued maintenance therapy with intermittent treatment in patients with remitted first episode schizophrenia who received maintenance therapy for only one year. Recurrence rates were significantly higher in the group receiving intermittent treatment than in the group that received continuous maintenance treatment. In the light of these results, indicating the importance of continuous treatment from the early phases of the disease onwards, we might wonder whether a LAI antipsychotic should be used already after the first episode of schizophrenia. In this regard, a recent observational community cohort study conducted in Finland [10] investigated the risk of rehospitalization and medication discontinuation in a nationwide cohort of 2,588 consecutive patients with schizophrenia who were hospitalized for the first time between 2000 and 2007. The authors reported that the use of LAI antipsychotic (haloperidol, risperidone, perphenazine, zuclopenthixol) was associated with substantially better outcomes than with the equivalent oral formulations.

LAI atypical antipsychotics in early psychosis

As for LAI atypical antipsychotics, there are currently very few data available on their use in first-episode schizophrenia.

An open-label study [11] conducted over two years in patients with first episode schizophrenia showed that those assigned to risperidone LAI had a significantly lower recurrence rate and a higher percentage of adherence compared to the control group treated with oral risperidone.

In another open-label study [12] conducted on patients with newly diagnosed schizophrenia or schizophreniform disorder, treatment for two years with risperidone LAI led to a remission in 64% of patients.

A RCT reported on the acceptance and the initial adherence outcomes with risperidone LAI treatment in patients with first episode schizophrenia [13]. Individuals who took risperidone LAI were significantly more likely to remain adherent at 12 weeks compared with patients treated with oral antipsychotics. These results support the feasibility and acceptability of LAI atypical antipsychotics as a treatment strategy already at the early stages of schizophrenia.

Duration of treatment

One of the open questions about how best to ensure the continuity of the treatment is the question of how long to treat patients in the maintenance phase of schizophrenia [1]. Based on evidence of clinical studies showing that even those patients who have been stable on antipsychotics for the period of two to five years after an acute episode relapse more frequently if they are taken off medication than if they continue it [14]. According to the guidelines of the Canadian Psychiatric Association [15] antipsychotic drugs for the treatment of

a first episode of psychosis should be continued for at least two years after the first symptom remission, while one should observe a minimum of five years of stability without relapses before making a slow withdrawal of antipsychotic drugs over a 6-24 months in patients with a history of previous recurrences.
As in the treatment of other chronic diseases, a significant problem with continued long-term antipsychotic treatment is that of undesirable effects of drugs. In addition to the well-known neurological side effects of typical antipsychotics, there is clear evidence of metabolic side effects associated with some atypical antipsychotics [16]. Some studies have also suggested that chronic exposure to antipsychotics may contribute to the reduction of the volume of brain tissue founf in the disease [17]. However, one study [18] conducted in patients with newly diagnosed schizophrenia verified that prolonged treatment with long-acting risperidone was associated with stability of white matter volume, in contrast to a volume reduction observed in patients treated with the oral formulation of the same drug; the study concluded that changing the adherence to risperidone may act on myelination and give reason for the better prognosis associated with the LAI antipsychotic than the oral formulation.
It is clear, however, that the risk-benefit ratio of long-term treatment should be carefully considered and that the clinician should be careful in prescribing the lowest dose of antipsychotic needed to control symptoms.

Adherence to treatment

One of the main factors that determine inadequate treatment and its untimely suspension is poor adherence to the treatment itself [3]. Poor adherence to medication is one of the most important problems in the treatment of patients with mental illness. The majority of hospital admissions are caused by some degree of non-adherence, although it is often unclear whether the non-adherence is causing a relapse or is a consequence of symptom worsening [19]. The percentage of patients with schizophrenia who are partially or completely non-adherent is estimated to vary between 40 and 60% [20].
Factors that contribute to poor adherence to drug therapy in schizophrenia are: patient-related factors (poor insight, depression, substance abuse), treatment-related factors (side effects, lack of efficacy, complexity of the regimen) and lack of support or therapeutic alliance with the doctor or the medical team [1]. Some of these factors can be acted upon by improving drug delivery strategies, such as with long-acting formulations. However, it should be kept in mind that for prompt recognition and correction of poor adherence educational efforts directed to patients and to medical staff are also extremely useful [21]. Poor adherence has been identified as an important risk factor for recurrence [3 22]. The use of LAI antipsychotics has been shown to improve adherence to treatment, leading to a lower percentage of drug withdrawal, relapse and hospitalization [23].

First generation and second generation antipsychotics

Although atypical antipsychotics are widely used, the debate over their alleged better tolerability compared to typical antipsychotics is still alive [24]. A meta-analysis by Leucht et al. [25] compared the effectiveness of nine atypical or second generation antipsychotics (SGAs) with first generation antipsychotics (FGAs) in patients with schizophrenia. The authors found that four of SGAs were better than FGAs for overall efficacy, with small to medium effect sizes (amisulpride, clozapine, olanzapine and risperidone). The other SGAs were not more efficacious than the FGAs, even for negative symptoms. Authors concluded that SGAs differ in many properties and are not a homogeneous class. The meta-analysis provides data for individualised treatment based on efficacy, side effects, and cost. Moreover the results from another recent meta-analysis [26] suggest that, whereas individually SGAs were not consistently superior to FGAs, as a group, SGAs were associated with less relapse, overall treatment failure and hospitalization than FGAs, having a modest but clinically relevant effect size.
In recent years, the propensity of atypical antipsychotics to induce weight gain and changes in glucose and lipid metabolism raised doubt about their alleged advantage over typical antipsychotics, leading to a reconsideration of the positioning of some atypical antipsychotics in the treatment of schizophrenia [27]. Overall, the results of recent analyses comparing typical and atypical antipsychotics demonstrate the high heterogeneity of the two classes of drugs, which does not allow any generalization. The choice of medication should be made on the basis of a careful assessment of each case, and of the various treatment options available [2].

LAI antipsychotics

LAI antipsychotics were introduced over 40 years ago for reasons of potential advantages compared

Table I. Benefits of LAI antipsychotics.

Assuring drug delivery in patients who are unreliable pill takers or are drug reluctant - better adherence
Early identification of non-adherence
Providing a mechanism for monitoring adherence with injections
No need to remember to take medication every day
Regular interactions between patient and medical staff
Reduced relapse frequency and rehospitalization rates
Clear attribution of the cause of relapse or non-response, discriminating between non adherence or lack of response
Reduce the risk of accidental or deliberated overdose
Treating patients with more stable plasma concentrations than oral medications
Avoidance of first-pass metabolism - better relationship between dose and blood level of drug
Lower and less frequent peak plasma level - reduced side effects

vs. their oral counterparts, including their ability to improve compliance and to distinguish between non-adherence and lack of response, and to monitor the regular contact between patient and their caregivers, to reduce the risk of accidental or deliberate overdose, to achieve better bioavailability and obtain a more predictable correlation between drug dosage and plasma concentrations [20]. Table I summarizes the benefits of LAI antipsychotics.

LAI antipsychotics, however, have also some limitations, such as slow dose titration, a greater time required to reach steady state, and side effects persisting for a while if they have to be suspended for safety concerns. Traditionally, LAI formulations are used in the maintenance treatment of patients with schizophrenia, usually after clinical stabilization with oral antipsychotics. More recently, LAI formulations of atypical antipsychotics, including risperidone, olanzapine, paliperidone and aripiprazole, have been developed [28]. Table II lists the characteristics of available LAI antipsychotics.

Efficacy and safety of LAI *vs.* oral antipsychotics

Although it is reasonable to expect that LAI antipsychotics, may improve the clinical outcome of schizophrenia by improving adherence to treatment, the evidence obtained over the years of wide spread use of LAI typical antipsychotics is not completely clear [35 36]. On the other hand, systematic analyses of the effectiveness of the recently introduced LAI atypical antipsychotics are still in progress. A series of analyses and systematic reviews of the literature has been conducted to compare the effectiveness of LAI atypical antipsychotics to both typical and atypical oral antipsychotics [37-39].

A large metareview [35], including 8 Cochrane reviews of RCTs of individual LAI antipsychotics in patients with schizophrenia or schizophreniform disorder found recurrence rates and tolerability of LAI antipsychotics to be similar to the oral medications, while overall clinical improvement was significantly more frequent and marked with LAI than oral antipsychotics.

The results of a systematic review [36], carried out to compare LAI typical antipsychotics with typical and atypical oral antipsychotics, showed an overall higher clinical benefit of LAI typical antipsychotics, but these results were highly variable and inconclusive mainly because of the heterogeneity of methods and interventions used in the various studies.

In a systematic review and meta-analysis of 10 RCTs of at least 12 months duration, published between 1975 and 2010, including a total of 1,700 patients, a significant reduction in relapse rate (21.6% *vs*. 33.3%, RR 0.70, 95% CI 0.57 to 0.87, p = 0.0009) and rate of dropouts for inefficacy of LAI antipsychotics compared to typical oral antipsychotics was demonstrated [37].

Another systematic review of studies published between 2000 and 2011 [38] that compared the efficacy of LAI and oral antipsychotics on relapse, hospitalization and discontinuation of drug for any cause in schizophrenia revealed a clear difference between observational studies (4 prospective and 4 retrospective), which showed a significant benefit for the LAI formulations (prospective studies: RR = 0.62, 95% CI 0.48-0.81, p < 0.001; retrospective studies: RR = 0.56, 95% CI 0.44 to 0.71, p < 0.001), and RCTs (5 studies), which showed a non-significant difference favouring LAI formulations (RR = 0.89, 95% CI 0.64 to 1.22, p = 0.416). The authors of this meta-analysis concluded that the study design may affect considerably the results obtained: in particular, the controlled clinical trials, while avoiding the confounding factors and selection bias often present in observational studies, do not take into account the characteristics and variability of setting of real world treatment.

In a recent meta-analysis by Kishimoto et al. [39] of 21 RCTs (n = 5,176 patients), LAI antipsychotics did not reduce relapse compared with oral antipsychotics in

schizophrenia patients. The exceptions were first-generation LAI antipsychotics, mostly consisting of fluphenazine-LAI studies, which were superior to oral antipsychotics regarding relapse and hospitalization. Considering these findings and in order to evaluate the real world effectiveness of LAI compared with oral antipsychotics, the authors underline the need of large and long pragmatic trials, which better represent common clinical practice.

Efficacy and safety of the individual LAI atypical antipsychotics

Risperidone LAI: despite some studies have demonstrated significant reductions in recurrence rates with the risperidone LAI formulation compared to the oral one [37 40-42] other studies have not confirmed this superiority [43-45]. The diverging results might be due to differences in quality, type of design and methods of the various studies [1].

Olanzapine LAI: the efficacy and tolerability of olanzapine LAI (olanzapine pamoate) was assessed by two randomized, double-blind, controlled trials, one compared to placebo [46], the other compared to oral olanzapine [47]. In the former olanzapine was significantly more effective than placebo in reducing scores on the PANSS (Positive And Negative Syndrome Scale); however, with a higher rate of side effects due to weight gain and alteration of lipid metabolism. The latter demonstrated a higher efficacy and tolerability of olanzapine LAI compared to oral olanzapine in the maintenance treatment of up to 24 weeks duration.

In an 8-week randomized, double-blind, placebo-controlled trial [48], olanzapine LAI improved the level of functioning in acutely ill patients with schizophrenia. In a recent 2-year, open-label, randomized study of olanzapine LAI, outpatients with schizophrenia maintained or improved their baseline level of functioning over time, but results did not significantly differ between olanzapine LAI and oral olanzapine [49].

Paliperidone LAI: several studies have demonstrated the greater efficacy of paliperidone LAI (paliperidone palmitate) compared to placebo and its non-inferiority compared to risperidone LAI in improving the scores of the PANSS in schizophrenia patients with acute symptomatology and a delay in time to recurrence in stabilized patients [50-52]. It should be noted that paliperidone LAI has a relatively neutral metabolic profile, resulting in only limited weight gain and no effects on glucose and lipid metabolism, both in short and long-term studies [53].

More recently, the LAI formulation of aripiprazole has been approved by EMA for the maintenance treatment of schizophrenia in adult patients stabilized with oral aripiprazole [34]. The clinical efficacy of aripiprazole LAI was established in two randomized, double-blind, controlled studies conducted in patients with schizophrenia. In one study [54], aripiprazole LAI was found to be non-inferior to oral aripiprazole for both the relapse rate and the PANSS change after 26 weeks of treatment. In the other study [55], the recurrence rate with aripiprazole LAI at 52 weeks was 5.03 times lower than with placebo. The main adverse events observed in the two clinical trials were: weight gain (9.0%), akathisia (7.9%), insomnia (5.8%), and pain at the injection site (5.1%). Furthermore, to evaluate the efficacy of aripiprazole LAI as an acute treatment in patients with schizophrenia, a 12 weeks double-blind RCT [56] was performed. The authors found that aripiprazole LAI improved symptoms and functioning in patients with acute schizophrenia, with acceptable safety and tolerability.

Current and recommended use of LAI antipsychotics

Current guidelines [2 14 15] generally recommend LAI antipsychotics for the maintenance treatment of schizophrenia among other available treatment options and/or when it is necessary to improve adherence to medication.

LAI antipsychotics can also be considered for the acute phase of schizophrenia if there is a repeated history of non-adherence or poor adherence [14], while data on the potential of new LAI formulations in the first episode of schizophrenia still appear to be too limited to represent the basis for specific recommendations [57]. However, many experts believe that these guidelines are too restrictive and that we should widen the indication of LAI antipsychotics in the treatment of schizophrenia [19]. With the increasing availability of effective and well tolerated LAI atypical antipsychotics, international guidelines should consider at which stage of the disease LAI atypical antipsychotics should be used, and which patients may benefit from treatment with such compound.

Another fact that has emerged from a number of surveys conducted in several Western countries, including Italy, is the relative lack of use of LAI antipsychotics even in patients who could clearly benefit from it. This finding may be explained by the number of misunderstandings and prejudices prevalent among physicians, patients and caregivers. LAI antipsychotics are gener-

Table II. Characteristics of LAI antipsychotics drugs.

Agent	Formulation	Release mechanism	Available doses	Injection site (IM) according to SPC	Starting modalities	
Fluphenazine decanoate [29]	Sesame oil solution (insoluble in water)	Prodrug: hydrolysis by esterases	25 mg/mL vials	Gluteal	Several strategies for the LD. OS not necessary	
Haloperidol decanoate [30]	Sesame oil solution (insoluble in water)	Prodrug: hydrolysis by esterases	50 mg/mL, 100 mg/mL vials	Gluteal	Several strategies for the LD. OS not necessary	
Risperidone LAI [31]	Aqueous suspension; risperidone encapsulated into biodegradable microspheres	Microspheres: diffusion and erosion	12.5, 25, 37.5 or 50 mg	Deltoid or gluteal	It is required a period of 3 weeks of overlap with oral risperidone	
Olanzapine pamoate [32]	Micro-crystalline salt of olanzapine and pamoic acid suspended in aqueous solution	Dissociation into olanzapine and pamoic acid	210, 300 or 405 mg	Gluteal	Several strategies for the LD	
Paliperidone palmitate [33]	Nanocrystal molecules in aqueous suspension	Poorly soluble in water: hydrolysis by esterases, dissociation into paliperidone and palmitic acid	39, 78, 117, 156 or 234 mg	Deltoid or gluteal	Initial injection on day 1 and day 8. OS not necessary	
Aripiprazole monohydrate [34]	Aqueous suspension; lyophilized powder of aripiprazole monohydrate crystals	Poorly soluble in water: crystals particles dissociate, with slow and prolonged dissolution and absorption	300 or 400 mg	Gluteal	OS is necessary for 2 weeks	

G: gauge; IM: intramuscular; LD: loading dose; OS: oral supplementation; SPC: Summary of Product Characteristics; TW: thin wall; UTW: ultra-thin wall.

ally considered as old and coercive drugs, and used to be reserved for patients with poor adherence, and have often been associated with a reduced involvement of the mental health staff in patient care [58]. Some psychiatrists consider them to be "a last resort" treatment, to be used when all other pharmacological therapies have failed, and reserve them for patients who have already presented with multiple episodes.

The high cost of LAI atypyical antipsychotics represent a further major obstacle to the prescription of these formulations. However, recent pharmacoeconomic studies have shown that LAI atypical antipsychotics may constitute a superior therapeutic strategy also from the economic point of view, if the various direct and indirect cost items of patients' care are taken into account [59].

Practical recommendations on the use of LAI atypical antipsychotics

There is large consensus among specialists that the optimal use of new formulation LAI require a substantial change in the general attitude towards the treatment with depot antipsychotics [1 19]. LAI atypical an-

	Injection interval	Dose range	T max	T ½ (multiple dosing)	Supply	Needle supplied or recommended	Storage	Monitoring post injection
	2-4 weeks	12.5-100 mg	0.3-1.5 days	14 days	Available in multi-dose vials	21 G	Refrigeration is not required; room temperature (15-30°C)	No
	4 weeks	50-200 mg	3-9 days	21 days	Available in multi-dose vials	21 G	Refrigeration is not required; room temperature (15-30°C)	No
	2 weeks	12.5-50 mg	21 days	3-6 days	Must be reconstituted: vial with microspheres and syringe with 2 ml of diluent	Deltoid: 21 G 1-inch (25 mm) UTW; Gluteal: 20 G 2-inch (50 mm) TW	Refrigeration is required; (2-8°C)	No
	2-4 weeks	150-405 mg	7 days	30 days	Must be reconstituted	19 G (38 or 50 mm)	Refrigeration is not required; room temperature (15-30°C)	Yes (3 hours)
	4 weeks	39-234 mg	13 days	25-49 days	Pre-filled syringes	Deltoid: 23 G 1-inch (25 mm) or 22 G 2 ½-inch (according to patient weight) Gluteal: 22 G 1 ½-inch (38 mm)	Refrigeration is not required; room temperature (15-30°C)	No
	4 weeks	300 or 400 mg	6.5-7.1 days	29.9-46.5 days	Must be reconstituted	21 G 1 ½-inch (38 mm) in non-obese patients; 21 G 2-inch (50 mm) in obese patients	Refrigeration is not required; room temperature (15-30°C)	No

tipsychotics should also be considered as a potential first choice and should be used for suitable patients whenever treatment is indicated in the long-term and not just for patients with poor adherence [2 19 60]. An effective pharmacological maintenance therapy is the starting point for success of multimodal treatment and rehabilitation programs for people suffering from schizophrenia. It is general expert consensus that oral antipsychotics should be initiated as soon as possible in patients with a newly and firmly diagnosed schizophrenia [2]. Even though the data on the effectiveness of LAI atypical antipsychotics in this area are still limited, it can be assumed that they are at least as favorable as oral antipsychotics. In patients with an acute exacerbation of schizophrenia, in which the treatment guidelines propose treatment with oral antipsychotics, the use of LAI atypical antipsychotics should be considered when these exacerbations are due to prior repetitive non-adherence or poor adherence [1].

Finally, it is worth recalling that the switch from an oral antipsychotic to a LAI formulation requires specific strategies to maintain or improve the therapeutic efficacy and to minimize the effects of a potential cholinergic or histaminergic rebound [61].

Conclusions

In conclusion, the recent emergence of LAI formulations of atypical antipsychotics has increased the treatment portfolio available for individualized and personalized treatment of schizophrenia, a long neglected key aspect in the management of patients with mental illness. Early intervention and continuity of treatment are decisive for achieving long-term remission, preventing a malicious course of the disease and reducing the costs and the burden of the disease. Traditionally, LAI have been reserved for non-adherent patients who have already experienced multiple episodes, The availability of new LAI drugs, with a better tolerability than the earlier typical depot antipsychotics in terms of extrapyramidal side effects, provides the option of extending such treatment to young patients in the initial stages of schizophrenia. This is particularly relevant considering the risk of relapse after discontinuation of treatment and the devastating consequences of a relapse. Further education of doctors and patients is needed to consider LAI antipsychotics from a new perspective: not any more as drugs of last resort, but rather a first step to achieve continuity of treatment and clinical remission. More well-designed long-term studies in first episode patients will be needed to confirm the preliminary, yet encouraging results with LAI formulations of atypical antipsychotics.

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