SOCIETÀ ITALIANA DI PSICHIATRIA

EVIDENCE-BASED PSYCHIATRIC CARE

OFFICIAL JOURNAL OF THE ITALIAN SOCIETY OF PSYCHIATRY

Editors-in-Chief
Emilio Sacchetti, Claudio Mencacci

Vol. 03 - Number 2/2017

Published by

PACINI EDITORE

ISSN 2421-4469

EVIDENCE-BASED PSYCHIATRIC CARE

OFFICIAL JOURNAL OF THE ITALIAN SOCIETY OF PSYCHIATRY

Editorial Office
Editors-in-Chief
Emilio Sacchetti - emilio.sacchetti@unibs.it
Claudio Mencacci - claudio.mencacci@gmail.com

Editorial coordinator and secretary
Lucia Castelli - lcastelli@pacinieditore.it
Tel. +39 050 3130224 - Fax +39 050 3130300

Managing Editor
Patrizia Alma Pacini

Publisher
Pacini Editore Srl
via Gherardesca1 - 56121 Pisa, Italy
Tel. +39 050 313011 - Fax +39 050 313000
www.pacinimedicina.it

Journal registered at "Registro pubblico degli Operatori della Comunicazione" (Pacini Editore Srl registration n. 6269 - 29/8/2001).

Registration in progress at the Tribunal of Pisa

CONTENTS

www.evidence-based-psychiatric-care.org

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.
   - Reviews, articles (both regular and short) and meet-the-expert should have summaries subdivided in the following sections: Objectives, Materials and Methods, Results, and Conclusions.
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.

The paper must be sent to:
lcastelli@paciniedITORE.it

INTRODUCTION

Emilio Sacchetti, Claudio Mencacci

Editors, Evidence-Based Psychiatric Care

Treatment of schizophrenia has recently undergone radical changes, not only in terms of our understanding and use of effective and appropriate interventions but also in shortening the gap between research and routine clinical practice. These aspects are very relevant as they reduce the gap between pure research and the real-world. A researcher can be a clinician, with all the intrinsic complexities that involves, and a clinician can contribute to the development of new knowledge that is useful for different cohorts of patients and in different settings of care. Ultimately, both evidence and experience find new and fruitful points of convergence that can lead to effective, appropriate and sustainable treatments and interventions. In this sense, psychiatry has become a modern science and assumes the contradictions and challenges of modernity by increasing its ability to pursue rehabilitative therapeutic approaches. Such changes allow for reflection on the different techniques and interventional settings:

- techniques are important in the effort to combine psychopharmacological, psychotherapeutic and psychosocial interventions into a truly integrated approach that considers real scientific evidence together with new clinical evidence (through practice monitoring tools, from clinical records to case reports and audit of clinical systems);
- interventional settings are important, not only as places, but also as networks and treatment pathways that are flexible in relation to the stage of disease, treatment goals, contexts and the individual characteristics of the patient.

In this sense, a 'new' clinic cannot avoid tests of its appropriateness. Such a concept in health care develops within the sphere of the epistemological theory of complexity and its effects in the field of public health. In this dimension, appropriateness emerges as an indispensable feature of health care interventions, integrating efficacy and efficiency, and can be defined as "a component of the quality of care that refers to the technical-scientific validity, acceptability and pertinence (relative to individuals, circumstances, places and the current state of knowledge) of health care". In particular, clinical appropriateness refers to the indication or performance of a health care intervention in a way that the chances of benefits outweigh the potential risks. If it is evident that ineffective intervention may not be appropriate, clinical appropriateness measures the individual effectiveness of the patient's needs and clinical complexity, as well as the expected effectiveness on population cohorts based on clinical issues, setting and abilities of health care systems.

Such a clinical approach departs from the limitations of merely waiting and becomes an active clinic, capable of combining an "individualized" approach with a "public health" approach, i.e. considering both public health and the population. It is capable of defining priorities, not only of an individual treatment but also of service policies; e.g. early

treatment and intervention in adolescence and pre-adolescence.
Thus, it is possible to assess the success of new approaches in adherence, patient knowledge and active participation of patients in treatment, as well as resistance to treatment (which cannot be easily explained by lack of response to a drug, but often by a complexity of genetic factors, on which significant results from pharmacogenomics research can be expected towards greater personalization of treatment, based on individual settings), "recovery", intended as finding oneself and in the experience of suffering and disease.
Thus, clinics will have to take greater responsibility in activating processes that give more weight to these issues, which may have the peculiar effect of breaking pessimistic and stigmatizing dogma regarding psychiatric disorders and psychiatric patients, which is still widespread in the population, and even among health care providers.
This clinic takes on the challenge of mind-body unity, considering various forms and pathways related to the organization of services, care and protection of the body: attention to lifestyle, especially in psychiatric patients with severe mental illness; complete protocols for monitoring side effects and/or adverse events, with attention to individual and hereditary risk factors as well as those related to treatment (from drugs to cognitive psychotherapies), refusing to refer to a hierarchy of "acceptability" of the disability, but defining it with the patient and his or her culture and identity.
Up to now, the main goal in the treatment of schizophrenia has been rapid reduction of symptoms in the short term and reducing the risk of recurrence, together with the burden on physical, social and economic factors, because recurrences and re-hospitalizations increase refractoriness to treatment, modify brain morphology and progressively reduce the possibility of the patient returning to baseline levels of functioning. However, the introduction of atypical or new-generation antipsychotics and long-acting injectable (LAI) formulations, such as the current available LAI (paliperidone palmitate) administered quarterly, has been, and will be, a remarkable step forward in the pharmacological approaches to schizophrenia. With this class of drugs, clinical trials have begun to look beyond pure symptomatic efficacy to include cognitive aspects, social functioning and quality of life, leading to the adoption of broader and more ambitious therapeutic targets. Indeed, today, remission of symptoms and, ultimately, functional autonomy and social functioning represent higher goals in the longer term, but nonetheless achievable in the treatment of schizophrenia. The picture that has emerged shows a significant advantage of maintenance therapy for schizophrenia, especially in terms of being more effective on negative and affective symptoms, recovery of social skills and reduction of adverse effects. Pharmacological treatment, in particular with atypical antipsychotics in LAIs, represents the therapeutic means to not only achieve remission but, together with psychosocial interventions such as family psycho-education, social skills training and cognitive behavioural therapy, also significantly decrease symptom recurrence and promote functional recovery of patients with the ultimate goal of rehabilitation.

PALIPERIDONE: THE EXPERT POINT OF VIEW

Paolo Girardi

Dipartimento di Neuroscienze, Salute Mentale e Organi di Senso, Sapienza Università di Roma, Facoltà di Medicina e Psicologia; Ospedale Sant'Andrea, Roma, Italia

The clinical and scientific interest for in paliperidone is the interest for an goes back to an antipsychotic drug line that was born began in 1958 with the discovery of haloperidol and reached now paliperidone, including antipsychotic drugs with a prevalent and constant antagonist action on the D2 receptors. The initial perception of paliperidone in clinical practice has evolved over time, both for both pharmacodynamic (antagonist action on 5-HT2A receptors, rapid drug-receptor dissociation) and pharmacokinetics reasons (width breadth of the therapeutic window, regular kinetics in the therapeutic range, stability of plasma concentrations, minimal hepatic metabolism, reduced interaction with other substances). Overall, these pharmacological characteristics guaranteed paliperidone a clinical ductility flexibility that risperidone itself didoes not present. Given its balanced, persistent and non-irreversible binding to D2 receptors, the high tolerability and low tendency to induce side effects, since its marketing paliperidone has represented an added value in to the treatment of psychosis since it came on the market.

In recent years, clinicians have also witnessed the advent of second-generation long-acting injectables (LAI) antipsychotics. With the introduction of a risperidone LAI formulation, there has been an improvement in adherence of among schizophrenic patients with schizophrenia as well as a reduction in relapses, both in terms of both frequency and intensity. Furthermore, the therapeutic relationships with the psychotic patients was have improved. This was an unprecedented unexpected phenomenon that did not occurred occur with haloperidol decanoate (as well as or with other first-generation depot antipsychotics), but that has occurred with all second-generation LAI antipsychotics. These observations have progressively prompted clinicians to change their perspective on the schizophrenic syndrome. Until then, in fact, tThe course and severity of this psychotic disorder were were previously evaluated mainly on the basis of positive symptoms (more evident), rather than on negative symptoms (difficult to investigate and intertwined with complex dimensions such as affectivity, cognitive functions and socialization). With the advent of second-generation LAI antipsychotics, it has been is understood that the more constant the anti-psychotic therapeutic dosage is constant, the more adaptive the mind-brain system will be. Therefore, the stability of the antipsychotic effect became a fundamental requirement for an effective reparative neuroplastic process. In From this new perspective, the advantages offered by LAI formulations of second-generation antipsychotics is are evident. In practice, the introduction of second-generation LAI antipsychotics has allowed clinicians to focus more on therapeutic programs that include social and emotional rehabilitation and patient empowerment. A patient is no longer "passivated", as in the past, but "empowered" and involved in care, in from a participatory perspective.

Today, like as yesterdaypreviously, the clinician to whom when a schizo-

phrenic patient with schizophrenia is referred with severe levels of psychotic dissociation is referred, the clinician first considers a drug with a predominant D2 receptor antagonist action. However, bBecause of previously shown its advantages, paliperidone is not only a the first-choice therapeutic option, but also offers the possibility of a rapid conversion to LAI treatment, both from with risperidone and from or oral paliperidone. The starting of tTreatment with paliperidone palmitate begins(which involves with two injections in the first eight 8 days) ; this usually allows a results in rapid reduction of positive symptoms and any preexisting side effects. In many cases, we observe the rapid passage transformation of the psychotic patient from a phase of simple compliance (often imposed), to a phase of "assisted" adherence (in which the patient is still supported, but already provides contributesa substantial consensus), to a phase of conscious adherence. From this point of view, an important advantage of paliperidone palmitate compared to with risperidone and oral paliperidone seems to be the induction of a greater and faster neuroplasticity, with a more rapid recovery of insight, that which allows the patient to participate in psychoeducation groups and programs of rehabilitation. The discovery of these clinical advantages of paliperidone palmitate occurred by serendipity: ; we started began with from the idea of creating a formulation that would guarantee a less harmful compliance compared to that of with the first-generation depot antipsychotics and instead we reached a completely different therapeutic option, which makes paliperidone palmitate a the first-choice treatment. Its particular pharmacokinetics and constancy of action allow the patient a possibility of to adapt and adaptation, of copinge, which in fact activates their resilience already from the acute phase. It is essential, therefore, the possibility of using that paliperidone palmitate is used, even without a preliminary stabilization with oral treatment in patients with schizophrenia who have previously responded to paliperidone or oral risperidone.

In conclusion, we can state that the antipsychotic effect of LAI treatment is based not only on the drug itself, but also on the constancy and stability of its action. These last features represent the true revolution of the care system. For this reason, many authors support the use of LAI antipsychotic therapy since from the first psychotic episode. Early treatmentActing on time, in fact, guarantees a fundamental qualitative effect: ; first the earlier we intervene on in the degenerative process connected to schizophrenia and the better the results will be. It is a therapeutic choice that represents the beginning of a new phase of life for the in the life of a person with schizophrenic persona from the point of view of planning, especially in view of the availability of paliperidone LAI in a quarterly formulation. The possibility to of implementing effective antipsychotic therapy with four injections per year will, in fact, drastically decrease the stigma associated with schizophrenia. The decrease in Reducing the stigma in surrounding the treatment of schizophrenia is a primary factor, not a secondary one, but a primary factor: reducing Reducing the number of administrations of antipsychotic therapy means decreasing the prejudices, increasing the scope and depth of the doctor-patient relationship, and focusing on rehabilitation work. This is a fundamental difference in the treatment of schizophrenia which, ultimately, can be implemented in a "repressive" sense, as in the case of high-dose haloperidol, or in the "expressive" sense, as in the case of paliperidone palmitate and other second-generation LAI antipsychotics.

SUCCESSFUL SWITCH FROM COMBINED TREATMENT WITH QUETIAPINE AND LITHIUM TO ARIPIPRAZOLE ONCE-MONTHLY (AOM) IN A PATIENT WITH SCHIZOAFFECTIVE DISORDER AND COMORBID COCAINE USE DISORDER

Angela Sabatino

Regina Coeli Correctional Medicine Unit, Rome Health Trust, Rome, Italy; Department of Mental Health, Viterbo Health Trust, Viterbo, Italy

A 50-year-old man came under care in September 2016 as an inmate of the Regina Coeli prison in Rome. He had been jailed on August 2016 and he was affected by asthma, childhood onset epilepsy, Insulin Dependent Diabetes Mellitus (IDDM) and HBV-HCV coinfection (since 1992). He presented with a history of intravenous cocaine abuse (since 1998), attempted suicide (in 2006) and cerebellar infarction (in 2014). Physical examination and laboratory tests on admission showed multiple self-harm scars and positive urine test for cocaine.

His medical and criminal history reported a treatment for cannabis abuse since the age of 24 and the use of intravenous cocaine since the age of 28. Although his criminal activity had begun even earlier, with car thefts, bank and apartment robberies, and drug dealing, he declared he was never under investigation or convicted for those crimes.

Later on, cocaine abuse triggered epileptic seizures and cerebellar infarction, causing him to be repeatedly hospitalized over the years, as well as systematically excluded by therapeutic community programs (as his case was labeled as a dual diagnosis). Eventually, his case was referred to the local mental health service to be taken into care with the ICD-9 diagnoses of schizoaffective and substance use disorder in borderline personality.

In 1994, the patient got a steady employment at the municipal waste management company. During the following 22 years, until his retirement due to the worsening of his many conditions (i.e., COPD, IDDM, schizoaffective disorder, liver cirrhosis), he reported particularly stressful life and work rhythms (“I never slept at night, I used to sleep during the day”). Over the years, he went through several psychiatric hospitalizations, some of which requested compulsory treatment. Of those, the most remarkable took place in 2008, following a suicide attempt by drug overdose.

At the time of admission to the prison, the patient was undergoing the following treatment: lithium carbonate 600 mg/day, gabapentin 900 mg/day, promazine 25 mg/day, quetiapine 600 mg/day, diazepam 12 mg/day. Laboratory tests on admission showed a serum lithium level of 0.40 mEq/L. Patient reported he had never had higher serum lithium level,

Corrispondenza

Angela Sabatino
sabatinoangela@gmail.com

even when he used to take lithium carbonate at the dosage of 900 mg per day. He did not show signs or symptoms of acute psychiatric disorders at the time of admission. Instead, he presented with a hyperthymic temperament, poor impulse control, and tendency to over-react. He also complained of insomnia and moderate levels of somatic anxiety.

After a few weeks of detention, the patient became progressively more depressed with rapid mood switches to elevated mood, irritability, dysphoria, and paranoid thoughts. He also engaged in a variety of self-injury behaviors (superficial cutting of the forearms) that requested seclusion. After a preliminary work to enhance therapeutic alliance (given the history of multiple treatment failures), the patient's treatment was changed by adding oral aripiprazole at the dose of 20 mg per day for the first two weeks, and 30 mg per day there after [1]. Simultaneously, sodium valproate was started at the dose of 500 mg per day, and quetiapine treatment was gradually discontinued.

A few weeks after the introduction of aripiprazole, the patient reported a substantial improvement of his mood with a reduction of anger and rumination about substance use [2 3]. Impulse control also improved, especially following the gradual titration of sodium valproate to 1500 mg per day. During the following weeks, gabapentin and promazine were gradually discontinued, while diazepam was cross-switched to lorazepam. After about three months, the patient was undergoing the following treatment: aripiprazole 30 mg/day, lithium carbonate 900 mg/day (serum lithium: 60 mEq/L), sodium valproate 1500 mg/day, lorazepam 7.5 mg/day.

Although symptom control and treatment adherence were satisfactory, a switch from oral to long-gacting injectable (LAI) formulation of aripiprazole was proposed in view of a future transition from the prison to a therapeutic community for dual diagnosis [4]. The patient agreed with the proposed change, especially in the perspective of further decreasing the pharmacological load due to concurrent medical conditions. In January 2017, the LAI treatment with AOM 400 mg was started and oral aripiprazole was easily discontinued over three weeks [5]. The worsening of a pre-existing lithium-related tremor was noticed after the third AOM administration so that a reduction in lithium dosage was agreed upon, especially considering the established mood stability, the patient's subjective well-being and the many comorbidities. Lithium carbonate was therefore slowly discontinued, while a treatment with lamotrigine (up to 200 mg per day) was gradually introduced. In February 2017, after checking for drug interactions, the patient was admitted to a program for HCV infection treatment with saclatasvir and sofosbuvir.

In March 2017, the patient developed a neurological syndrome characterized by drowsiness, confusion, lethargy, short-term amnesia, and ataxia. Blood tests showed an ammonemia of 145 mcg/dL (normal range: 27-90 mcg/dL). The syndrome was treated by infusing saline solution and branched-chain amino acids. Although hyperammonemia remitted in a few days and was likely caused by the HCV-related liver cirrhosis, a gradual discontinuation of sodium valproate was undertaken to exclude its possible role in the onset of the syndrome.

Over time, the initial compliance to therapy evolved to an active adherence, with the patient determined to maintain the established treatment because of the well-being he was experiencing, especially in terms of physical health (i.e. better glycemic control, improvement of liver function due to the reduced pharmacological load).

Because pre-existing tremor remained the only significant treatment side-effect, an attempt to reduce AOM regimen to 300 mg/month was made with no benefit. Conversely, the AOM dosage reduction led to a relapse of mood symptoms such as irritability and dysphoria. Therefore, the treatment with AOM 400 mg/month was promptly restored, one more time achieving clinical remission. At present, after four months (AOM steadystate), the patient maintains clinical remission and reports subjective well-being and treatment satisfaction by underlining the balance between stabilization and vitality achieved for the first time with AOM.

In this case, the effort towards a personalized treatment, the good therapeutic alliance, and the availability of a safe and tolerable LAI antipsychotic treatment in the context of a comprehensive rehabilitation program seem to have led to an optimal clinical outcome.

References

1. McRae-Clark AL, Verduin ML, Tolliver BK, et al. *An open-label trial of aripiprazole treatment in dual diagnosis individuals safety and efficacy* J Dual Diagn 2009;5:83-96.
2. Beresford TP, Clapp L, Martin B, et al. *Aripiprazole in schizophrenia with cocaine dependence: a pilot study*. J Clin Psychopharmacol 2005;25:363-6.
3. Brown ES, Jeffress J, Liggin JD, et al. *Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole*. J Clin Psychiatry 2005;66:756-60.
4. Martínez JS, Caballero AR. *Long-acting aripiprazole in comorbid bipolar disorder and borderline personality disorder and substance abuse.* J Clin Psychopharmacol 2017;37:266-7.
5. Abilify Maintena US (aripiprazole) (2016). Full prescribing information. Tokyo, Japan: Otsuka Pharmaceutical Co. Ltd.