SOCIETÀ ITALIANA DI PSICHIATRIA

EVIDENCE-BASED PSYCHIATRIC CARE

OFFICIAL JOURNAL OF THE ITALIAN SOCIETY OF PSYCHIATRY

Editors-in-Chief
Emilio Sacchetti, Claudio Mencacci

Contents

Vol. 01/02 - Number 3/4/2015-1/2016

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 S.p.A.
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 SpA 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 above-mentioned 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

TO LIBERALIZE OR NOT TO LIBERALIZE THE RECREATIONAL USE OF CANNABIS: THIS IS NOT THE QUESTION

Emilio Sacchetti, Claudio Mencacci

Editors-in-Chief,
Evidence-Based Psychiatric Care;
Past President and President of the Italian Society of Psychiatry

Despite years of war on its distribution, cannabis continues to be the most widely used substance of abuse in the world after alcohol, caffeine and tobacco. In practice, there is no nation that has not passed a law aimed at regulating the recreational use of cannabis. However, the legal consequences established by different countries are far from standardized; the use of street cannabis is variably considered to be legal or essentially legal, decriminalized, illegal but often unenforced, and, more commonly, illegal (Fig. 1). Furthermore, this scenario has not yet stabilized. In the last few years, some nations have re-examined their laws regulating the recreational use of cannabis and others are now considering this. In Italy, the current discussion is focusing on the pros and cons of changing from a decriminalized position to legal consumption.

Overall, the regulations on how to counteract the diffusion of street cannabis are largely written in the water because, despite years of passionate debate, there is no evidence that one option is unequivocally preferable to another. Therefore, the decision to liberalize or not to liberalize the recreational use of cannabis is essentially based on political considerations.

From a medical perspective, however, there is no doubt that cannabis has negative effects on human health and that the search for relationships between current regulations on the recreational use of cannabis and medical sequelae related to its consumption will have pivotal consequences on public health policies. From the point of view of health care, mental health reasonably has a major role. This conclusion does not come exclusively from the well-documented potential of cannabis to induce use disorders. Although a causal link has not been definitively proven, a large and continuously increasing body of evidence demonstrates that cannabis users have structural and functional abnormalities on brain imaging; develop acute and possibly long-lasting impairment of learning, memory and attention; frequently show apathy and avolition that may contribute to educational, social and volitional underachievement; are more prone to traffic accidents, and present an appreciable risk for the development of severe mental illnesses over time, particularly full-blown schizophrenia and schizophrenia spectrum disorders [1].

Taken together, these facts show that psychiatrists are in the firing line of the detrimental effects of cannabis. Nevertheless, psychiatry has until now been excluded, at least in Italy, from official decisions and planning on the diffusion of street cannabis and the management of the associ-

Correspondence

Emilio Sacchetti
emilio.sacchetti@unibs.it

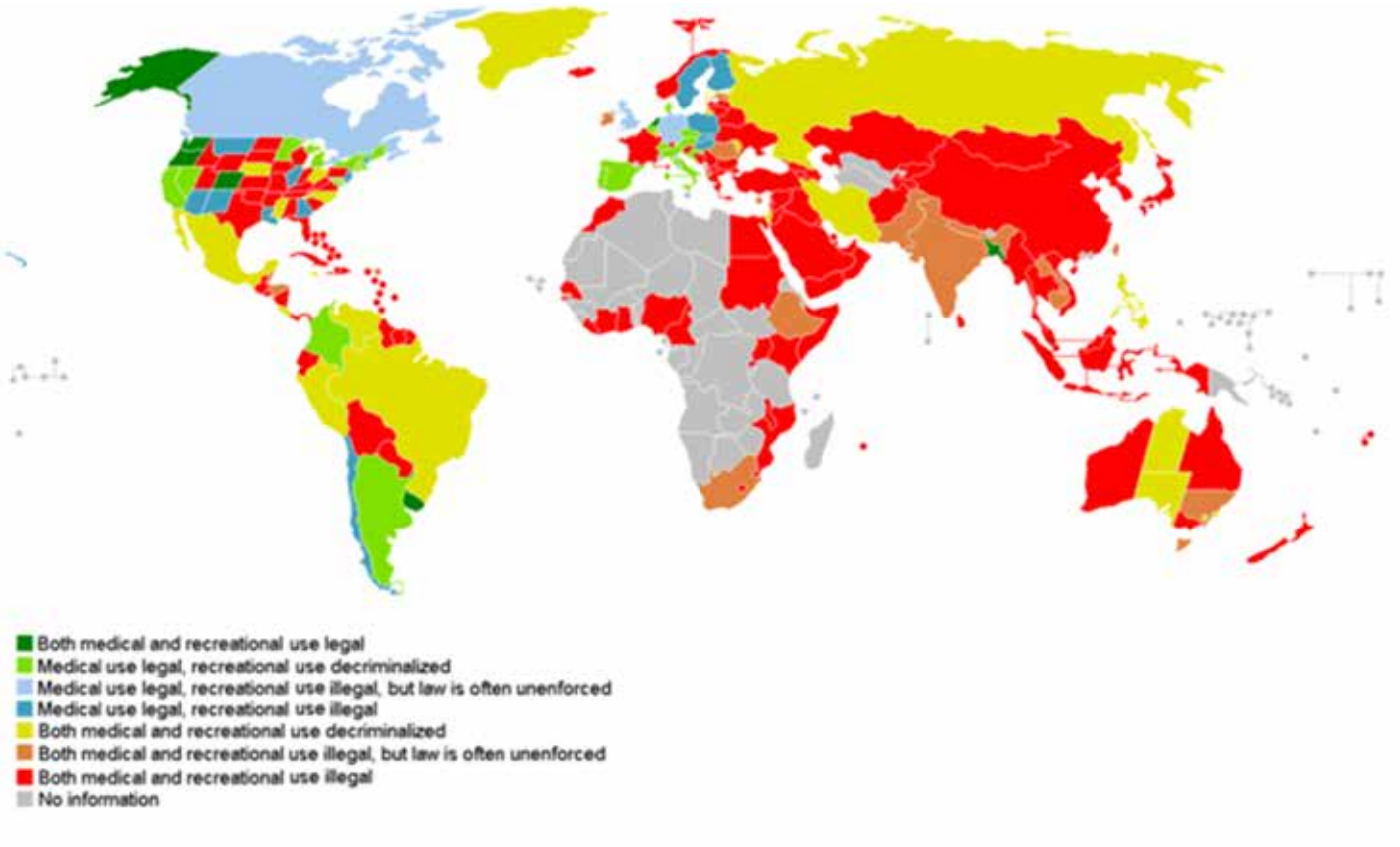


FIGURE 1.
World Map showing the legal status of cannabis for medical and recreational purposes by country. Source: Wikipedia, the free encyclopedia. Date 30 January 2016. Source Own work Author Povke19991211.

ated clinical problems. Therefore, the Italian Society of Psychiatry (SIP) formally affirm their right and obligation to play a leading role in the current Italian debate on changing from the current decriminalized position of today to free access to the use of cannabis for recreational purposes. The SIP, as a professional institution, refutes any suggestion that they hold the balance in relation to the politicians' final decision but rather offers its competence and cooperation for constructive discussion and optimized application of the law, whatever it will be.

Acknowledging that the point of departure for an honest debate on the legal aspects related to the recreational use of cannabis is that both street cannabis and cannabis-related psychiatric problems are increasing phenomena, the SIP can begin by presenting a number of crucial issues, some of which apply to decriminalized and legal use of street cannabis, whereas others are especially important in the event of liberalization.

With regard to both decriminalized and liberalized use of street cannabis, educational campaigns unequivocally based on the message that recreational consumption of cannabis, especially when frequent and heavy, is bad, and sometimes extremely bad, for mental health are an absolute priority. Due to ignorance, ingenuity, party spirit or a mixture of these factors, too much of the current information on street cannabis continues to offer the idea that use of cannabis is substantially risk free. It is also important that the educational messages are systematically included in broader campaigns stressing that any distinction between hard and soft substances is not only scientifically indefensible but also misleading for promoting balanced and responsible opinions on the recreational use of substances in general. Good educational campaigns must be even stronger, if possible, in the event of liberalization of the recreational use of cannabis; otherwise, liberalization risks creating public opinion that the so-called soft substances are safe and confusion between the recreational and therapeutic use of cannabis. On the contrary, we are well aware that the two uses are incomparable and require independent rules. Support for an unequivocal separation between the two uses of cannabis may also be inferred, for example, from the sharp contrast in the literature showing that lower potency cannabis preparations are associated with therapeu-

tic potential and the clinical experience showing that the negative health effects of cannabis increase with increasing potency [2].

Another hot topic involves the health consequences associated with the recreational use of cannabis during adolescence. Many independent lines of evidence underline that the unhealthy effects of cannabis are maximized during adolescence. However, although essential, educational campaigns for adolescents are not enough to protect against street cannabis. Therefore, it is absolutely essential that the correct information on the recreational use of cannabis is coupled with the resolution to prosecute with severe sentences those who are caught pushing to young people.

It is essential that the issue of the potency of legal cannabis is resolved before any law on liberalization comes into force. Two main types of evidence lead to this conclusion. The first is that, in many countries, the concentration of Δ^9-tetrahydrocannabinol has increased over the years to the point that it is difficult to consider the cannabis of today as the same cannabis as at the start of the millennium. For example, in the last 20 years, the percentage of Δ^9-tetrahydrocannabinol has increased almost three-fold in the United States, and contemporaneously the Δ^9-tetrahydrocannabinol/cannabidiol ratio has changed from approximatively 15 to almost 80.[2] Second, evidence once again from the United States underlines that samples from states that allow the use of cannabis have a much higher percentage of Δ^9-tetrahydrocannabinol than samples from prohibitionist states.[2] This observation strongly supports the inference that laws on recreational use of cannabis affect the potency of street cannabis. Thus, it seems therefore realistic to suggest the parallel illegal market will quickly try to retain customers by offering street cannabis with a higher potency than the legal substance. In order to counteract this risk, two principal strategies may be hypothesized. The first implies a head-to-head competition between legal and illegal cannabis sales that will lead to an endless race to increase the potency of cannabis; this option is clearly unacceptable in practice for obvious ethical and medical reasons. The other strategy implies pre-identifying an unequivocal cut-off for the maximum content of Δ^9-tetrahydrocannabinol allowed in legal cannabis and putting the necessary deterrents in place against the sale of street cannabis with a higher potency.

If and when legal cannabis enters the market, it is also highly recommended that, like cigarettes, the packages highlight that the recreational use of cannabis is associated with increased probabilities of mental deficit and disorders.

Furthermore, it is essential that any law regulating the recreational use of cannabis states in advance the funds to be assigned to psychiatry for supporting clinical governance, pre-clinical and clinical research, and educational campaigns. A law promoting the legal recreational use of cannabis could easily allow funding to be raised from the sale of cannabis. In turn, more restrictive laws would allow money to be shifted from the budget used for fighting the distribution of cannabis. In any case, politicians must keep in mind that the best way to counteract the recreational use of cannabis lies in education. Funds for education are therefore a top priority.

Last but not least, the passage from decriminalized use to liberalized recreational use of cannabis has the relevant added value of making tenable comparative studies on the incidence of cannabis-related clinical events that occur under the two different regulatory regimens. Such as research strategy could help to define once and for all a truly evidence-based preference between liberalized and decriminalized recreational use of cannabis. To miss such an opportunity could be a mortal sin.

References

1 Volkow ND, Swanson JM, Evins AE, et al. *Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review*. JAMA Psychiatry 2016;73:292-7.

2 ElSohly MA, Mehmedic Z, Foster S, et al. *Changes in cannabis potency over the last 2 decades (1995-2014): analysis of current data in the United States*. Biol Psychiatry 2016;79:613-9. doi:10.1016/j.biopsych.2016.01.004.

Rafael Penadés[1,2*], Helena Pérez-García[3], Alexandre González-Rodríguez[1], Rosa Catalán[1,2], Miguel Bernardo[1,2]

[1] Barcelona Clinic Schizophrenia Unit (BCSU), Institut Clínic de Neurociències (ICN), Hospital Clinic, Barcelona, Spain; [2] Department of Psychiatry and Clinical Psychobiology, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain; [3] Hospital Institut d'Assistència Sanitària, Salt, Spain

TREATING COGNITION IN SCHIZOPHRENIA: SEARCHING FOR THE BEST EVIDENCE-BASED PRACTICES

Abstract

Objectives: Treating cognition in schizophrenia has been one of the major challenges in psychiatry during the last decades. Developing medications and cognitive therapies to treat the cognitive deficits associated with schizophrenia is a high priority.

Methods: A critical review of the bibliography has been performed. We focused on some aspects like the choice for best evidence-based practices in clinical practice that remain as an open questions.

Results: Cognitive remediation therapies seem to have beneficial effects on cognitive global functioning and psychosocial functioning. Unfortunately, cognitive remediation is not recommended by international guidelines because there are still some open questions regarding generalisation to daily functioning and no widely accepted cognitive remediation approach. Combining cognitive remediation and pharmacotherapy is an interesting line but it still has not been well studied. Besides, there are currently no indicated cognitive-enhancing drugs.

Conclusions: All in all, at the present time cognitive remediation can be considered as possibly the best evidence-based intervention to treat cognition in schizophrenia.

Key words: Schizophrenia, Cognition, Cognitive Remediation, Pharmacotherapy, Cognitive-enhancing drugs

Introduction

Treating cognition in schizophrenia has been one of the major challenges in psychiatry during the last decades, as the cognitive impairment has been reported to be a major determinant of clinical outcomes in this population [1]. Approximately 75-85% of patients with diagnosis of schizophrenia suffer from impairment in cognition and that has been associated with negative outcomes, low rates of medication compliance and higher rates of psychotic relapses, in particular in first-episode patients with psychosis [2-3]. Thus, developing medications and cognitive therapies to treat the cognitive deficits associated with schizophrenia is a high priority. At the same time, some aspects like the choice for best evidence-based practices in clinical practice have not been so well studied.

Pharmacotherapy

Pharmacotherapy interventions, such as antipsychotic treatments, have been reported to be effective in treating positive symptoms in schizophrenia [4], although studies focusing on the efficacy of antipsychotics on cognitive deficits have shown controversial results [1 2 5]. This lack of

Correspondence

Rafael Penadés
rpenades@clinic.ub.es

effective treatment strategies has encouraged recent research to investigate the underlying neurobiological mechanisms involved in cognitive impairment in schizophrenia [3 6]. Further, this need of biological research has led to the MATRICS initiative (Measurement and Treatment Research to Improve Cognition in Schizophrenia) to identify seven cognitive domains that should be addressed as molecular targets for treating cognition in schizophrenia [3,6]. These domains included working memory, attention and vigilance, processing speed, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition.

In this line, recent research has identified different molecular targets that would be implicated in the development of new drug strategies for the treatment of cognition in schizophrenia [6 7]. These molecular targets include cholinesterase inhibitors (e.g. rivastigmine, donapezil, galantamine), nicotinic and muscarinic receptor agonists, glutamatergic targets (e.g. glycine site agonists, glycine reuptake inhibitors, metabotropic receptor agonists), antipsychotics with affinity for dopamine D4 receptors, psychostimulants (e.g. inhibitors of COMT), serotonergic targets (e.g. serotonin partial agonists) and modafinil [3 7].

A recent meta-analysis investigated the efficacy of adjunctive pharmacotherapy for cognitive deficits in schizophrenia [5]. Acetylcholinesterase inhibitors, such as rivastigmine and donepezil, were reported to have a positive effect on verbal learning and memory, but, unfortunately, with a moderate significance, and non-stable effects on spatial learning and memory [5]. The same authors reported that glutamatergic medications and serotonergic agonists had a small effect-size improvement in psychotic symptoms, but no effects for cognitive symptoms, suggesting that the combination of antipsychotics and these drugs would not be useful in treating cognitive impairment in schizophrenia [5].

With regard to the effects of antipsychotics on cognitive impairment in schizophrenia, a recent meta-analysis compared the efficacy of antipsychotics on overall cognition, as well as on specific cognitive domains [8]. The authors found that treatment with quetiapine, olanzapine and risperidone was associated with better improvement in overall cognitive scores compared to amisulpride and haloperidol. Further, quetiapine, olanzapine and risperidone were better than amisulpride in terms of executive functions, and quetiapine had better positive effects on attention and processing speed tasks than the other antipsychotics. These findings support the notion that significant differences in cognitive effects can be found between antipsychotics according to specific cognitive domains. The median duration of included trials was around 52 weeks [8].

In summary, acetylcholinesterase inhibitors have shown a marginal improvement in verbal learning and memory when cognitive remediation therapy is not provided. Other cholinergic, glutamatergic and serotonergic drugs would have no effects on the specific cognitive domains, as defined by the MATRICS initiative. When focusing on the effects of antipsychotics, quetiapine and olanzapine were found to have the most positive effects.

Cognitive Remediation Therapies

Cognitive remediation therapy for schizophrenia is a behavioural training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization, as defined at the Cognitive Remediation Experts Workshop (Florence, Italy, April 2010) [9]. Thus, cognitive remediation is a psychological therapy that aims to enhance cognition with a further goal that improved cognition will affect community functioning [9].

A range of cognitive remediation programs have been developed and evaluated over the past 40 years. After a period of time with non-conclusive studies, we have now meta-analytic studies with positive results [9-11]. Meta-analytic studies are considered to be the highest level of evidence in the evidence-based medicine. Thus, one recent meta-analysis [9] was based on 40 studies with 2104 patients and it concluded that cognitive therapies produce long-lasting improvements on cognitive global functioning in patients diagnosed with schizophrenia. Cognitive remediation is efficacious in improving global cognition (Cohen's d = 0.448). Particularly, significant benefits for the majority of cognitive domains were found as in attention (d = 0.250), speed of processing (d = 0.258), working memory (d = 0.346), verbal learning and memory (d = 0.410), problem solving (d = 0.572) and social cognition (d = 0.651). The effect was significant after the follow-up (d = 0.428). There also were significant benefits for symptoms (d = 0.177) and functioning (d = 0.418). Fortunately, at follow-up the effect was still significant for functioning but not for symptoms. Finally, results did not seem to be affected by study methodology.

Nonetheless, in despite of having an amount of studies focused on efficacy, there still are some many other data that deserve a deeper analysis in order to

help clinicians to provide best evidence-based services. Firstly, a greater effect on psychosocial functioning when patients received cognitive remediation together with an adjunctive psychiatric rehabilitation compared to cognitive rehabilitation alone. Secondly, the use of a more strategic cognitive remediation approach would be more useful to improve daily functioning. Recently, it has been suggested that drill and practice and strategy learning could be complementary and maybe they have their specific effects on outcome. Thus, drill and practice training programs seem to be more frequently used for neurocognitive deficits and strategy learning for functional disability [12]. However, studies using drill and strategy could have a particular interesting impact on other variables outside of cognition, such symptoms of quality of life [12]. Finally, cognitive remediation was more effective when patients were clinically stable.

In summary, recent reviews indicated that cognitive remediation therapy produced beneficial effects on cognitive global functioning and psychosocial functioning on the patients diagnosed with schizophrenia. Furthermore, the type of therapy plays an important role for generalization the outcomes than duration therapy or type of presentation.

Combining pro-cognitive drugs and cognitive therapies

Traditionally, clinicians focused on two different strategies: pharmacotherapy or cognitive therapies when treating cognition in schizophrenia patients. Nonetheless, in order to find new evidences able to improve our clinical practice, the therapeutic approaches maybe should diverge from the prevailing models (antipsychotics and cognitive therapies) and focus instead on a different and more practical treatment strategy. Swerdlow [13] has proposed a new framework accounting for the following elements:

- antipsychotic medications to constrain the scope and severity of psychotic exacerbations and thereby facilitate engagement in cognitive rehabilitation;
- cognitive therapies designed to engage healthy neural systems to compensate for and replace dysfunctional higher circuit elements;
- medications that specifically target cognitive mechanisms engaged by these rehabilitative psychotherapies.

In this approach, the importance to combine CRT, antipsychotics and pro-cognitive pharmacology is emphasised. Swerdlow [14] suggests that specific pro-cognitive drugs could be ineffective when administered without the demands of cognitive therapies and nonetheless they can still be effective when delivered together with CRT as a synergy facilitator. Swerdlow [14] proposed the lack of efficacy of pro-cognitive drugs could be due to the fact that those trials have being done using drugs that were designed to surmount neuropathological changes in schizophrenia (e.g., D-cycloserine) [15]. An alternative strategy is suggested: using medications that enhance spared neural functions in these patients. Unfortunately, evidence showing the existence of those 'spared' healthy circuitries is still scarce and for that reason some specific research is needed. Such new approaches would require a revision of regulatory guidelines to make such trials feasible and economically possible.

Controversies and open questions

Positive results for cognitive therapies have been shown in different randomised and controlled trials and also in meta-analytic studies. Although that is encouraging evidence, there are still some controversial and open questions. To start with, a number of studies with negative results have been published [16-18]. Thus, in order to avoid negative results something must be learned about those studies with negative results, for instance they tend to be based on computer programs with few participation of the therapist. Moreover, even when results are able to improve cognition it seems that not all treatments are able to translate this improvement into functional benefits. Further studies examining the generalisation of cognitive improvement to functioning are needed. Another important question is about the so-called practice effect. Practice effect is a consequence of the familiarity with test instructions, and it is likely for individuals to obtain higher scores on many measures upon repeated testing. Thus, the effect of practice in cognitive assessment has to be taken into account when outcomes of different studies are considered. Goldberg et al. [19] showed a gain of 0.36 effect size (Cohen's d) upon repeat testing in a composite global cognition measures in a first-episode of psychosis patients treated with second-generation antipsychotics. Similarly, a comparison sample of healthy controls showed an observed effect size gain of 0.33. Thus, the practice effect has to be taken into account because different treatments could not be exceeding the expected practice effects (Figure 1).

Furthermore, some other barriers might be preventing researchers and clinicians to get better empirical

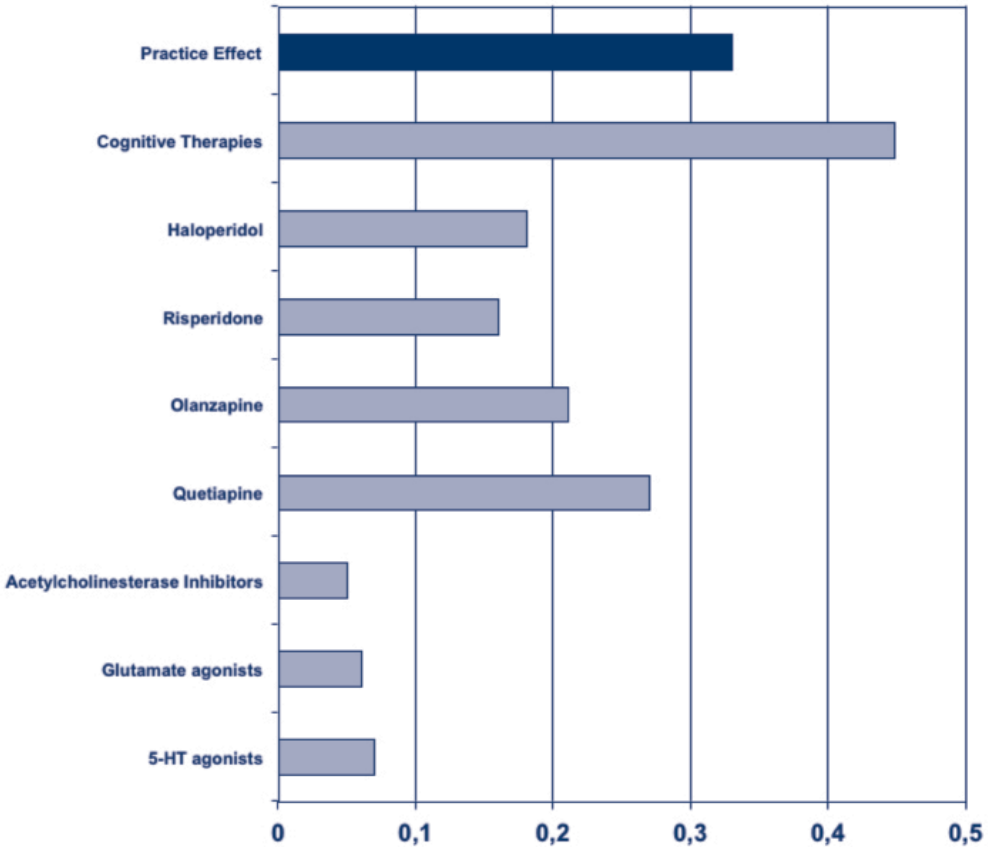


FIGURE 1.

Comparison of the effect sizes of different treatments and practice effect. Effect sizes has been calculated over whole cognition by de Cohen's d. Results have been taken from the meta-analyses by Choi et al.[5], Wykes et al.[9] and the study by Goldberg et al.[19] for the practice effects.

evidence. Bromley [20] has suggested three of the problems regarding the use of cognitive enhancers in the treatment of schizophrenia that still remain controversial. Firstly, ecological validity of cognitive constructs. It seems like constructs researchers use to describe cognition are not always totally equivalent to the cognitive skills and behaviours that clinicians see in their clinics. Secondly, perceptions of cognitive impairments show an intriguing discrepancy between patients and clinicians. That can be particularly problematic, for instance discrepancy between objective and subjective assessments can complicate some practical aspects as monitoring cognitive-enhancer medication. Thirdly, after cognitive treatment improvements in functionality are expected by patients and clinicians. However, even though that is a desirable gain, assessments of patients functional status may not be the best way to establish the cognitive-enhancers' efficacy. Functionality is a very complex variable and also a considerable amount of variables can be mediating in the relationship between cognition and functioning. In the next future, research on mediators between cognition and functioning should help us to have a better understanding about more complex assessment strategies in the frame of empirical mediation models.

Finally, one great challenge is the use of cognitive-enhancer medication in combination with cognitive therapies. However, this strategy will predictably be difficult to implement in clinical practice. For instance, it is necessary to know exactly when the cognitive-enhancing drug should be administered relative to cognitive remediation. Michalopoulou [21] has discussed this topic indicating that all drugs show changing plasma levels through the day and ideally cognitive remediation should have to coincide with the time window of maximal plasticity enhancement by the cognitive-enhancing drug. At this moment independent measures of the plasticity window and therefore drug plasma levels serve as the most relevant proxy are not available. Besides, it is important to consider potential harms of these drugs, for example interactions with antipsychotic medications, substance abuse, or other unknown effects. Information regarding actual use of the cognitive-enhancers, their security and benefit balance and potential harms are harshly lacking [22].

Conclusion

There are currently no indicated cognitive-enhancing drugs and no widely accepted or applied cognitive remediation approach. Cognitive remediation therapies have beneficial effects on cognitive global functioning and psychosocial functioning on the patients diagnosed with schizophrenia. Unfortunately, cognitive remediation is not recommended by international guidelines because there are still some open questions regarding generalisation to daily functioning. Nonetheless, at the present time cognitive remediation can be considered as probably the best evidence-based intervention to treat cognition in schizophrenia.

Take home messages for psychiatric care

- Evidence-based therapies for treating cognition in schizophrenia are highly warranted
- Cognitive remediation has beneficial effects on cognitive global functioning and psychosocial functioning, possibly, being the best evidence-based intervention when treating cognition in schizophrenia
- Effectiveness of combination of cognitive remediation and pharmacotherapy seems to be still unclear

References

1 Minzenberg MJ, Carter CS. *Developing treatments for impaired cognition in schizophrenia*. Trends Cogn Sci 2012;16:35-42.

2 Keefe RS, Buchanan RW, Marder SR, et al. *Clinical trials of potential cognitive-enhancing drugs in schizophrenia: what have we learned so far?* Schizophr Bull 2013; 39:417-35.

3 Vingerhoets WA, Bloemen OJ, Bakker G, et al. *Pharmacological interventions for the MATRICS cognitive domains in schizophrenia: what's the evidence?* Front Psychiatry 2013;4:157.

4 Lewis DA. *Pharmacological enhancement of cognition in individuals with schizophrenia*. Biol Psychiatry 2011;69:397-8.

5 Choi KH, Wykes T, Kurtz MM. *Adjunctive pharmacotherapy for cognitive deficits in schizophrenia: meta-analytical investigation of efficacy*. Br J Psychiatry 2013;203:172-8.

6 Gray JA, Roth BL. *Molecular targets for treating cognitive dysfunction in schizophrenia.* Schizophr Bull 2007;33:1100-19.

7 Goff DC, Hill M, Barch D. *The treatment of cognitive impairment in schizophrenia*. Pharmacol Biochem Behav 2011;99:245-53.

8 Désaméricq G, Schurhoff F, Meary A, et al. *Long-term neurocognitive effects of antipsychotics in schizophrenia: a network meta-analysis*. Eur J Clin Pharmacol 2014;70:127-34.

9 Wykes T, Huddy V, Cellard C, et al. *A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes.* Am J Psychiatry 2011;168:472-85.

10 McGurk SR, Twamley EW, Sitzer DI, et al. A *meta-analysis of cognitive remediation in schizophrenia*. Am J Psychiatry. 2007;164:1791-802.

11 Katsumi A, Hoshino H, Fujimoto S, et al. *Efficacy of cognitive remediation in schizophrenia: a short review of its variable effects according to cognitive domain.* Open J Psychiatr 2015;5:170-6.

12 Paquin K, Larouche A, Cellard C, et al. *A systematic review on improving cognition in schizophrenia: which is the more commonly use type of training, practice or strategy learning?* BMC Psychiatry 2014:14:139.

13 Swerdlow NR. *Are we studying and treating schizophrenia correctly?* Schizophr Res. 2011;130:1-10.

14 Swerdlow NR. 2012. *Beyond antipsychotics: pharmacologically-augmented cognitive therapies (PACTs) for schizophrenia*. Neuropsychopharmacology. 2012;37:310-1.

15 Gottlieb JD. Cather C, Shanahan M, et al. *D-cycloserine facilitation of cognitive behavioural therapy for delusions in schizophrenia.* Schizophr Res 2011;131:69-74.

16 Wölwer W, Frommann N, Halfmann S, et al. *Remediation of impairments in facial affect recognition in schizophrenia: efficacy and specificity of a new training program*. Schizophr Res 2005;80:295-303.

17 Dickinson D, Tenhula W, Morris S, et al. *A randomized, controlled trial of computer-assisted cognitive remediation for schizophrenia.* Am J Psychiatry 2010;167:170-180.

18 Gomar JJ, Valls E, Radua J, et al. *A multisite, randomized controlled clinical trial of computerized cognitive remediation therapy for schizophrenia.* Schizophr Bull 2015; In press May 25. pii: sbv059.

19 Goldberg TE, Goldman RS, Burdick KE, et al. *Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect?* Arch Gen Psychiatry 2007; 64: 1115-1122.

20 Bromley E. *Barriers to the appropriate clinical use of medications that improve the cognitive deficits of schizophrenia*. Psychiatr Ser 2007;58:475-481.

21 Michalopoulou PG, Lewis SW, Wykes T, et al. *Treating impaired cognition in schizophrenia: the case for combining cognitive-enhancing drugs with cognitive remediation.* Eur Neuropsychopharmacol. 2013;23:790-8.

22 Nutt D, Gispen-de Wied CC, Arango C, et al. *Cognition in schizophrenia: summary Nice Consultation Meeting 2012.* Eur Neuropsychopharmacol. 2013;23:769-78.

ILLNESS INTRUSIVENESS IS ASSOCIATED WITH DEPRESSION SEVERITY AMONG PATIENTS WITH UNIPOLAR DEPRESSIVE DISORDERS

Alice Fattori [1], Luca Neri [2], Antonello Bellomo[3], Marco Vaggi[4], Claudio Mencacci [5] and the Improving Life for DEpression (ILDE) Study Group[6]

[1] Department of Clinical Sciences and Community Health, University of Milan, Italy; Légein Radicati Liberi srl, Milan, Italy; [2] Outcomes Research Consulting, Milano, Italy; [3] Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy; [4] Department of Mental Health, ASL 3, Genoa, Italy; [5] Depression Unit, Neuroscience Department, Fatebenefratelli Hospital, Milan, Italy; [6] Centers participating in the Improving Life for DEpression (ILDE) Study Group are listed in Appendix I

Abstract

Purpose: We sought to characterize the relationship between depression severity and illness intrusiveness in a large sample of outpatients with major depression disorders.

Method: Six hundred ninety-two patients with unipolar depressive disorders recruited in 19 Italian centers answered a self-administered survey including sociodemographic and clinical data. Illness Intrusiveness Ratings Scale (IIRS). A psychiatrist completed a standardized data collection form concerning depression severity (MADRS).

Results: According to MADRS score. 12.7% of patients were on clinical remission. 34.8% had mild symptoms. 44.4% had moderate severity. and 8.1% had severe depression. Significant predictors of IIRS global scores were frequency of physical exercise (β = -5.86; p = 0.02). number of drugs prescribed (β = -4.06; p<.0001). frequency of relapses in the past 10 years (β = -4.77; p = 0.02). primary psychiatric diagnosis (β =-5.64; p=0.03). Effect size of depression severity for each IIRS total scale was ω^2 = 0.24 and ω^2 = 0.16 for unadjusted and adjusted models respectively. Patients in clinical remission reported a mild level of distress on all IIRS scales (IIRS = 33.8; IIRS:ins = 2.50; IIRS:int = 2.92; IIRS:dev = 2.58).

Conclusion: We found a strong graded association between depression severity and life style disruptions in all dimensions of the Illness Intrusiveness Rating Scale. Our results suggest a persistent residual impairment even after partial or complete clinical recovery. Polypharmacy strongly contributes to life domains' disruption. thus suggesting further efforts to reduce regimen complexity.

Key words: Depressive disorders, illness intrusiveness, depression severity, MADRS

Introduction

There is substantial evidence that adaptations of patients' everyday activities. interests and life-styles to both treatment and disease factors (Illness Intrusiveness) partially mediate the effect of chronic medical conditions on subjective well-being and perceived-health among patients with different medical conditions [1-3]. Previous studies have shown that psychiatric conditions including obsessive-compulsive disorder and other anxiety syndromes impose dramatic limitations to patients' life and are felt as intrusive as life threatening diseases such as acquired immunodeficiency infection and cancer [1].

Depression is a primary determinant of years lost due to disability[4] and exerts a detrimental impact on functional impairment and health-related quality of life (HRQOL) compared to the general population and other

Correspondence

Luca Neri
luca_neri_4@hotmail.com

medical conditions [5-8]. Additionally previous studies have found that depression severity is strongly associated with functional disability [9 10].
Despite depressive symptoms had often been implicated as a mediator in the relationship between chronic medical condition and health-related quality of life impairment. the relationship between the severity of depressive symptoms and illness intrusiveness among working-age adults with major depressive disorder (MDD) is still scarcely characterized. Hence. we sought to characterize the relationship between depression severity and illness intrusiveness in a large sample of outpatients with major depression disorders.

Methods

Participants and Setting

ILDE study was carried out between June and July 2013 in 19 outpatient referral centers for diagnosis and treatment of psychiatric disorders across all Italian regions. Patients referred to the centers for psychiatric conditions were screened for eligibility by a psychiatrist during a regular follow-up visit at the clinic. We included adult patients with a clinical diagnosis of depression with the exclusion of bipolar disorders. According to International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD10; WHO. 1990) classified diagnosis in our sample were: Adjustment Disorder (AD; ICD10:F43.2). Dystimia (DYS. ICD10:F34.1). Recurrent Depressive Episode (RDE; ICD10:F33). Depressive Episode (DE; ICD10:F32). Mixed Anxiety and Depressive Disorder (ADD; ICD10:F41.2). Other Persistent Mood Disorder (OTHER; ICD10:F34.8. F34.9). Patients completed a self-administered questionnaire while the same psychiatrist recorded relevant clinical characteristics in a standardized data collection form. To preserve anonymity of data collection while matching clinical and patient-reported information. the psychiatrist handed the data collection form to the patient at the end of the visit. The patients sealed both the data collection form and the self-administered questionnaire in an anonymous envelope to return to the research team.

Measures

Depression severity

The Montgomery-Asberg Depression Rating Scale [11] (MADRS) consists of ten rating items that can be clinician-administered in a short period of time. Each item is scored on a 0-6 scale. with 6 indicating maximum symptom severity; the total score is constructed by summing the ten item scores. The ten items were designed to track treatment change; hence. the MADRS provides a sensitive instrument for measuring patient responses to antidepressant medications and other treatments [12 13]. According to the score. depression severity was classified as remission (MADRS: 0-6). mild (MADRS: 7-19). moderate (MADRS: 20-34). severe (MADRS: ≥ 35).

Illness intrusiveness

Illness intrusiveness results from disease- and treatment-induced disturbance on every-day life. activities and interests. The Illness Intrusiveness Ratings Scale [14] (IIRS) is a self-report questionnaire built on 13 items that ask respondents the extent to which their “illness and/or its treatment” interfere with 13 life domains central to quality of life. Each item ranges from 1 (not very much) to 7 (very much). Subscales are “Relationships and Personal Development”. “Intimacy”. and “Instrumental” life domains.

Demographic and Medical Information

The survey included a section on sociodemographic characteristics. Patients’ age. gender. Body Mass Index. frequency of physical activity. education level. marital status were recorded. Employment. inactivity. retirement. and unemployment status were classified using the International Labour Office definition[15]. Medical information included number of depressive episodes in the last ten years. time since disorder onset. number of comorbidities in the last twelve months. specifications about therapy and drugs prescribed.

Statistical Analysis

Analyses were conducted with SAS 9.2. Means and standard deviations or absolute and relative frequencies were computed for continuous or categorical variables. respectively. The association between MADRS score classes and socio-demographic characteristics has been evaluated with 1-way ANOVA or χ^2 test. The association between MADRS score classes and cognitive impairment was evaluated with χ^2 test. The unadjusted and adjusted association between outcomes and MARDS has been assessed with generalized linear models. We used an identity or logarithmic link function were appropriate depending on outcomes distribution for each analysis. We adjusted each model for socio-demographic characteristics (age. gen-

der. education. occupation. marital status) and clinical characteristics (disease vintage. treatment. primary diagnosis. number of comorbidities. BMI). P < 0.05 was considered statistically significant.

Results

Sample Characteristics

Sample characteristics are shown in Table I. The mean age was 46.0 ± 10.9 and the majority of patients were women (n = 446; 65.3%). Among 692 patients with complete MARDS scores. 12.7% were on clinical remission. 34.8% had mild symptoms. 44.4% had moderate severity. and 8.1% had severe depression. There were 188 patients with no or mild cognitive impairment (27.2%). 487 with moderate impairment (70.4%) and 17 with severe impairment (2.5%). We found a strong association between attention deficits and MADRS scores (no/mild impairment: 9.6 ± 6.9; moderate impairment: 23.4 ± 8.7; severe impairment:

Table I. Sample characteristics across classes of depression severity.

	Depression severity					
Characteristics	**Whole sample N = 692**	**Remission N = 88**	**Mild N = 241**	**Moderate N = 307**	**Severe N = 56**	
Socio-demographic	N (%) or mean (STD)					p
Age						0.43
< 40	186 (26.9)	25 (28.4)	69 (28.6)	80 (26.1)	12 (21.4)	
40-50	175 (25.3)	26 (29.6)	66 (27.4)	71 (23.1)	12 (21.4)	
> 50	331 (47.8)	37 (42.0)	106 (44.0)	156 (50.8)	32 (57.2)	
Women	440 (65.2)	55 (64.7)	142 (61.2)	202 (66.7)	41 (74.5)	0.26
Tertiary education	118 (17.0)	19 (21.6)	47 (19.5)	46 (15.0)	6 (10.7)	0.18
Living with partner	381 (55.9)	52 (59.8)	133 (56.1)	167 (55.3)	29 (52.7)	0.83
Children	442 (63.9)	58 (65.9)	142 (58.9)	203 (66.1)	39 (69.6)	0.24
Employment						0.29
Employed	339 (49.0)	52 (59.1)	117 (48.6)	141 (45.9)	29 (51.8)	
Inactive	177 (25.6)	14 (15.9)	62 (25.7)	84 (27.4)	17 (3.0)	
Retired	61 (8.8)	5 (5.7)	20 (8.3)	31 (10.1)	5 (8.9)	
Unemployed	115 (16.6)	17 (19.3)	42 (17.4)	51 (16.6)	5 (8.9)	
Physical activity (≥ 3 days/week)	83 (12.0)	23 (26.1)	38 (15.8)	22 (7.2)	0	<0.01
Clinical						
Years since diagnosis	6.3 (7.3)	5.0 (5.6)	6.3 (6.9)	6.4 (7.5)	7.1 (9.8)	0.33
Recurrent depression (≥ 3 episodes/10 years)	302 (46.3)	26 (29.9)	90 (39.6)	157 (54.9)	29 (55.8)	<0.01
Primary diagnosis						0.01
AD	53 (7.7)	11 (12.5)	22 (9.1)	18 (5.9)	2 (3.6)	
DYS	53 (7.7)	7.0 (8.0)	14 (5.8)	28 (9.12)	4 (7.14)	
RDE	298 (43.0)	33 (37.5)	88 (36.5)	149 (48.5)	28 (50.0)	
DE	122 (17.6)	12 (13.6)	46 (19.1)	48 (15.6)	16 (28.6)	
ADD	154 (22.2)	22 (25.0)	65 (27.0)	61 (19.9)	6 (10.7)	
Other	12 (1.7)	3 (3.4)	6 (2.5)	3 (1.0)	0	
Other Axis I diagnoses	34 (4.9)	6 (6.8)	21 (8.7)	7 (2.3)	0	<0.01
Body Mass Index						0.13
Underweight	22 (3.2)	0	12 (5.0)	8 (2.6)	2 (3.7)	
Normal weight	366 (53.7)	55 (63.2)	131 (55.0)	149 (49.2)	31 (57.4)	
Overweight	214 (31.4)	23 (26.4)	73 (30.7)	105 (34.6)	13 (24.1)	
Obesity	80 (11.7)	9 (10.3)	22 (9.24)	41 (13.5)	8 (14.8)	
N. of comorbidities	0.92 (1.20)	0.77 (1.03)	0.84 (1.18)	0.98 (1.27)	1.14(1.38)	0.04

	Depression severity					
Comorbidities:						
None	344 (49.7)	45 (13.0)	126 (36.6)	148 (43.0)	25 (7.27)	0.66
Serious injuries	18 (2.60)	3 (3.41)	4 (1.66)	8 (2.61)	3 (5.36)	0.43
Surgery	57 (8.24)	2 (2.27)	25 (10.4)	24 (7.82)	6 (10.7)	0.10
Osteo-articular	97 (14.0)	9 (10.2)	30 (12.4)	49 (16.0)	9 (16.1)	0.44
Hypertension	87 (12.6)	6 (6.82)	20 (8.30)	53 (17.3)	8 (14.3)	<0.01
CAD	7 (1.01)	0	5 (2.07)	1 (0.33)	1 (1.79)	0.14
Other CVD	26 (3.76)	3 (3.41)	6 (2.49)	12 (3.91)	5 (8.93)	0.15
Diabetes	28 (4.05)	3 (3.41)	5 (2.07)	17 (5.54)	3 (5.36)	0.21
Thyroid diseases	54 (7.80)	7 (7.95)	13 (5.39)	30 (9.77)	4 (7.14)	0.30
Dyslipidemia	44 (6.36)	5 (5.68)	13 (5.39)	19 (6.19)	7 (12.5)	0.26
Anemia	14 (2.02)	1 (1.14)	5 (2.07)	8 (2.61)	0	0.56
CKD	3 (0.43)	0	2 (0.83)	1 (0.33)	0	0.66
Lung diseases	18 (2.60)	1 (1.14)	6 (2.49)	5 (1.63)	6 (10.7)	<0.01
Gastrointestinal	66 (9.53)	10 (11.4)	25 (10.4)	23 (7.49)	8 (14.3)	0.21
Other	59 (8.53)	9 (10.2)	22 (9.13)	26 (8.47)	2 (3.57)	
Therapy						0.08
Pharmacotherapy	565 (81.6)	72 (81.8)	183 (75.9)	262 (85.3)	48 (85.7)	
Psychotherapy	11 (1.59)	2 (2.27)	8 (3.32)	1 (0.33)	0	
Drugs & psychotherapy	101 (14.6)	12 (13.6)	43 (17.8)	40 (13.0)	6 (10.7)	
None	15 (2.17)	2 (2.27)	7 (2.90)	4 (1.30)	2 (3.57)	
Association regimens (≥ 2 prescription drugs)	464 (67.0)	40 (45.5)	142 (58.9)	237 (77.2)	45 (80.4)	<0.01
N. of drugs	1.98 (1.01)	1.59 (0.97)	1.70 (0.87)	2.24 (1.00)	2.41 (1.20)	0.02
Antidepressant therapy						
NASSA	36 (5.20)	3 (3.41)	10 (4.15)	20 (6.51)	3 (5.36)	0.53
SSRI	390 (56.4)	44 (50.0)	149 (61.8)	169 (55.1)	28 (50.0)	0.14
SARI	21 (3.03)	2 (2.27)	4 (1.66)	11 (3.58)	4 (7.14)	0.15
SNRI	145 (20.9)	23 (26.1)	42 (17.4)	68 (22.1)	12 (21.4)	0.32
TCA	47 (6.79)	5 (5.68)	7 (2.90)	29 (6.45)	6 (10.7)	0.01
Other	48 (6.94)	2 (2.27)	10 (4.15)	27 (8.79)	9 (16.1)	<0.01
Other psychotropic drugs						
Anti-anxiety	388 (56.1)	35 (39.8)	121 (50.2)	195 (63.5)	37 (66.1)	<0.01
Anti-epileptics	97 (14.0)	8 (9.09)	26 (10.8)	52 (16.9)	11 (19.6)	0.06
Neuroleptics	131 (18.9)	15 (17.1)	24 (9.96)	78 (25.4)	14 (25.0)	<0.01

Antidepressant Therapy: NASSA: Noradrenergic and Specific Serotonin Antidepressants; SSRI: Selective serotonin reuptake inhibitors; SARI: Serotonin antagonist and reuptake inhibitors; SNRI: Serotonin-Norepinephrine Reuptake Inhibitors; TCA: Tricyclic antidepressants. Primary Psychiatric Diagnosis. AD: Adjustment Disorder (ICD10:F43.2); DYS: Dystimia (ICD10:F34.1); RDE: Recurrent Depressive Episode (ICD10:F33); DE: Depressive Episode (ICD10:F32); ADD: Mixed Anxiety and Depressive Disorder (ICD10:F41.2). Other Persistent Mood Disorder (OTHER; ICD10:F34.8. F34.9). P values represent confidence levels of χ^2 for categorical variables. one-way ANOVA for continuous variables.

34 ± 6.7. p for trend < 0.01; r = 0.71. p < 0.01). RDE was the most frequent diagnosis (43%). followed by mixed anxiety and depressive disorder (22%) and single major depressive episode (17%). The average duration of depression was 6.28 ± 7.34 years and 58% of patients consulted more than one physician after symptoms onset before receiving a diagnosis of depressive disorder. More than 45% (n = 302) of subjects had more than 2 major depressive episodes in the previous 10 years. Combined pharmacological

treatment and psychotherapy were prescribed in a minority of cases (14%). About half of the sample had no comorbid condition (n = 344; 49.7%). Patients with severe depressive symptoms had a higher number of comorbidities (1.14 *vs* 0.77. p for linear trend = 0.04). received more complex treatment regimens (80.1% *vs* 45.5%. p < 0.01). had more depressive episodes (55.8% *vs* 29.9%. p for trend < 0.01). more likely were occupationally inactive (30.4% *vs* 15.9%. p for trend < 0.05). carried out less physical activity (0% *vs* 26.1%. p for trend < 0.01). and had lower education (graduates: 10.7% *vs* 21.6%. p for trend < 0.05) compared to patients in clinical remission (Table I). Patients with RDE and DE had more severe symptoms compared to patients with ADD. AD. DYS or other depressive disorders (Table I. p < 0.011).

Socio-Demographic and Clinical correlates of Illness Intrusiveness

The pattern of association observed was partially different across subscales of illness intrusiveness (table 2). Global scores were associated with the frequency of physical exercise. the number of psychotropic drugs prescribed in the treatment regiment. the frequency of relapses in the past 10 years. the primary psychiatric diagnosis and was marginally associated with patients' employment status. The personal development scale was associated with physical exercise. the number of psychotropic drugs prescribed in the treatment regiment. the frequency of relapses in the past 10 years. the primary psychiatric diagnosis. patients' employment status. and was marginally associated with patients' marital status. The intimate relationship scale was associated with physical exercise. the number of psychotropic drugs prescribed in the treatment regimen and was marginally associated with the frequency of relapses in the past 10 years and the presence of children in the household. The instrumental domain subscale was associated with the number of comorbidities. the number of psychotropic drugs prescribed in the treatment regimen. the frequency of relapses and was marginally associated with patients' employment.

Depression Severity and Illness Intrusiveness

The average IIRS scores in the whole sample and

Table II. Socio-Demographic and Clinical Correlates of Illness Intrusiveness.

	IIRS	IIRS: Ins.	IIRS: Int.	IIRS: Dev.
Demographics		β (p)		
Age	-0.06 (0.51)	-0.01 (0.29)	-0.01 (0.32)	-0.00 (0.97)
Women	1.89 (0.27)	0.13 (0.35)	0.02 (0.92)	0.20 (0.16)
Living with partner	-2.75 (0.16)	-0.23 (0.14)	0.14 (0.50)	-0.31 (0.06)
Children	1.04 (0.63)	-0.01 (0.97)	-0.41 (0.07)	-0.04 (0.81)
Employed	-3.19 (0.05)	-0.24 (0.07)	-0.10 (0.55)	-0.30 (0.03)
Clinical				
Primary diagnosis				
AD	-0.41 (0.90)	0.01 (0.96)	0.12 (0.74)	-0.12 (0.67)
DYS	-0.89 (0.79)	-0.35 (0.19)	0.20 (0.58)	0.08 (0.77)
RDE	0.15 (0.94)	-0.07 (0.68)	0.05 (0.81)	0.07 (0.71)
DE	5.64 (0.03)	0.18 (0.40)	0.62 (0.03)	0.58 (0.01)
ADD	ref	ref	ref	ref
Other depressive syndromes	9.44 (0.21)	0.44 (0.46)	1.26 (0.11)	0.78 (0.22)
Recurrent depression (≥ 3 episodes/10 years)	4.77 (0.02)	0.34 (0.04)	0.41 (0.06)	0.38 (0.03)
Physical Activity (≥ 3 days/week)	-5.86 (0.02)	-0.24 (0.22)	-0.52 (0.04)	-0.60 (0.004)
Number of psychotropic drugs	4.06 (<0.01)	0.36 (<0.01)	0.23 (<0.01)	0.30 (<0.01)
Number of comorbidities	0.48 (0.50)	0.16 (<0.01)	-0.06 (0.41)	-0.03 (0.62)

Coefficient estimates and p values are based on generalized linear models (normal distribution with identity link function). For continuous variables. association estimates represent the change in the IIRS score associated with a 1-point increase in the independent variable. For categorical variable. association estimates represent the difference in the IIRS score between patients with a characteristic compared to the reference category.

Table III. Illness intrusiveness scale and subscales mean scores in the whole sample and across levels of depression severity.

		Depression Severity					
	Whole N = 692	Remission N = 88	Mild N = 241	Moderate N = 307	Severe N = 56		
HRQOL score	Unadjusted Mean Scores					ω2	P
IIRS	49.0	30.4	44.9	54.8	64.6	0.24	< 0.01
IIRS: development	3.7	2.3	3.4	4.1	5.0	0.21	< 0.01
IIRS: intimacy	4.1	2.7	3.7	4.5	5.1	0.12	< 0.01
IIRS: Instrumental	3.7	2.3	3.4	4.2	4.9	0.22	< 0.01
HRQOL score	Adjusted Mean Scores a					ω2	P
IIRS	48.6	33.8	47.5	55.6	64.7	0.16	< 0.01
IIRS: development	3.67	2.50	3.54	4.18	4.97	0.14	< 0.01
IIRS: intimacy	3.99	2.92	3.94	4.69	5.19	0.09	< 0.01
IIRS: Instrumental	3.72	2.58	3.67	4.24	4.89	0.13	< 0.01

Unadjusted and adjusted mean scores and p values are based on generalized linear models (normal distribution with identity link function); ω2 represents effect size for the F-test. Adjusted model included age. gender. tertiary education. presence of partner. number of children. employment status. recurrent episodes. physical activity. number of drugs. Body Mass Index. duration of disorder. number of comorbidities).

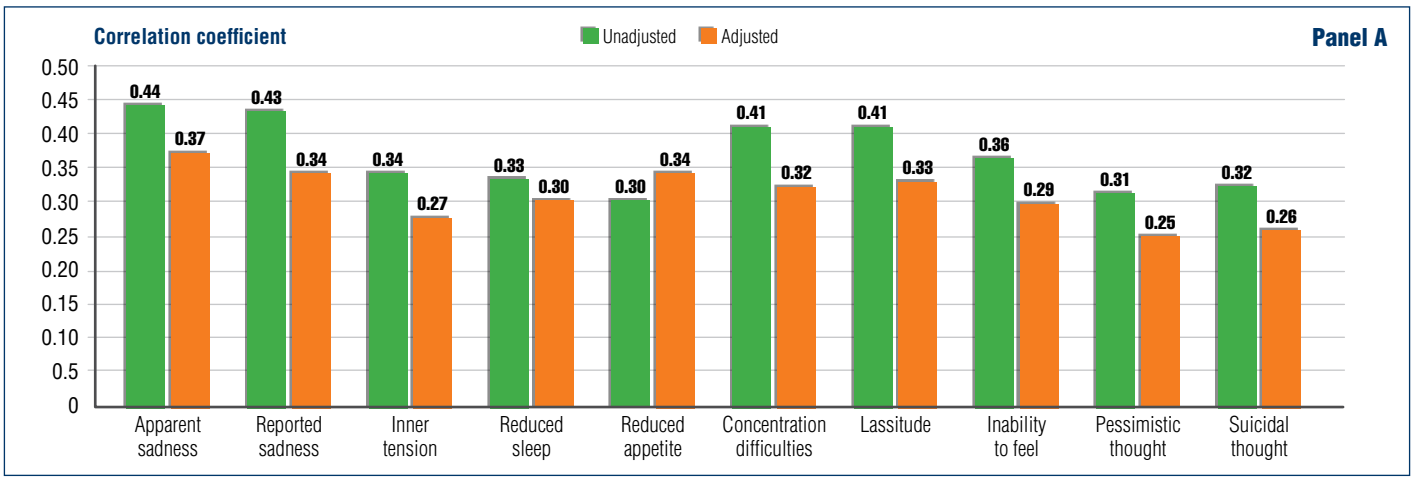
across MADRS classes are reported in Table III. We found a strong. graded association between depression severity and each HRQOL outcome. These associations were robust to adjustment for several confounders (Table III). The interaction between MADRS classes and diagnostic groups was not statistically significant and was removed from the model (not shown). Effect sizes in the full model ranged between $\omega^2 = 0.12$ (IIRS: intimacy subscale) and $\omega^2 = 0.24$ (IIRS: total score). To further explore the association between MADRS scores and IIRS. we evaluated the relationship between individual facets of depression and patients' perception of life-limitation (Figure 1).

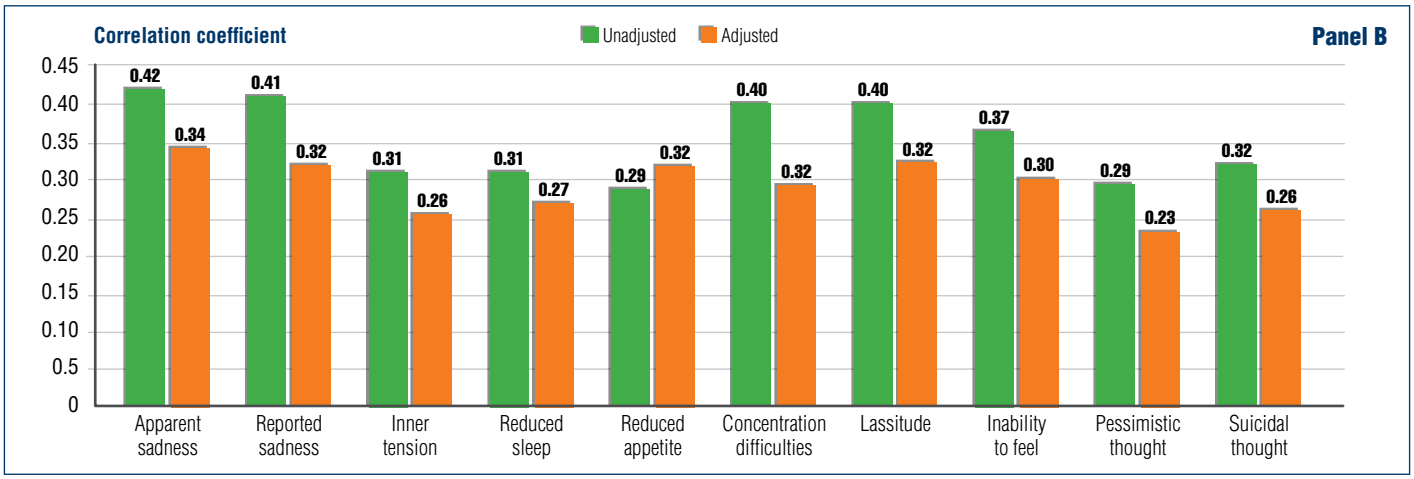
Discussion

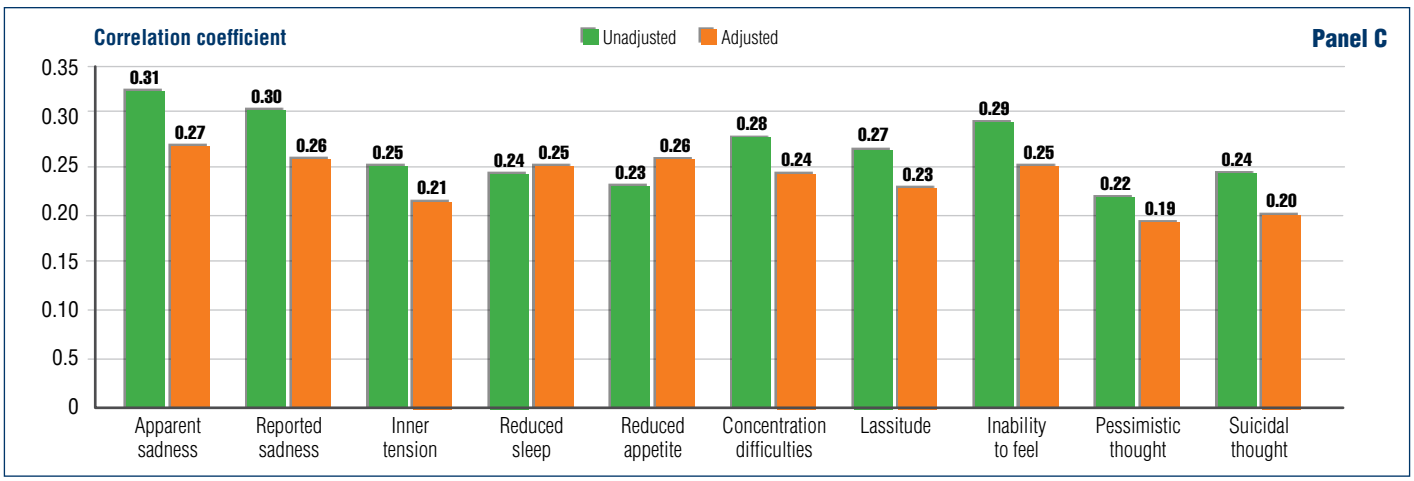
The primary objective of our study was to characterize the relationship between symptoms severity and perceived Illness Intrusiveness in a large national sample of working age patients with major depressive disorders. The results outlined the disruption of symptoms severity on patients life domains pivotal to health-related quality of life such as intimate relationships. personal development. work and social participation. Depression in the IIRS literature has been primarily studied as a specific complication of other disabling diseases and is considered a key mediator of subsequent quality of life impairment [16 17]. Indeed. depressive mood is common in chronic and life-threatening disease. as a result of illness-induced disruptions to lifestyle. activities. and interests [18-20].

We advanced current knowledge concerning the relationship between depressed mood and quality of life by demonstrating a strong graded association between depression severity and life-style disruption in all dimensions tapped by the Illness Intrusiveness Rating Scale. We observed a large effect size of depression severity for each IIRS total scale. both in the unadjusted ($\omega^2 = 0.24$) and adjusted ($\omega^2 = 0.16$) models. Adjusted IIRS mean scores in the whole sample (48.6) was higher compared to those found among patients with other severe chronic diseases such as bipolar disorder (43.8). multiple sclerosis (42.6). epilepsy (38.8). rheumatoid arthritis (37.9) end stage renal disease (38.8)[21 22]. To our knowledge. patients with severe symptoms showed the highest IIRS score compared to any other chronic condition investigated so far [3 22]. Further. we found that MDD patients on clinical remission still reported a mild level of distress on all IIRS scales. These subjects (mean IIRS: 33.8) scored similarly to patients with Insomnia (mean IIRS: 34.9) and Biliary cirrhosis (mean IIRS: 32.2)[22]. Our findings are consistent with previous research suggesting that a residual impairment of patients' functioning persists even after complete clinical recovery [23-26].

Interestingly. we found no evidence that any MADRS attribute drives the association between depression severity and IIRS. Our results suggest that all fac-


Correlation coefficient
Unadjusted
Adjusted
Panel A
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.5
0
0.44 0.37
0.43 0.34
0.34 0.27
0.33 0.30
0.30 0.34
0.41 0.32
0.41 0.33
0.36 0.29
0.31 0.25
0.32 0.26
Apparent sadness
Reported sadness
Inner tension
Reduced sleep
Reduced appetite
Concentration difficulties
Lassitude
Inability to feel
Pessimistic thought
Suicidal thought


Correlation coefficient
Unadjusted
Adjusted
Panel B
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.5
0
0.42 0.34
0.41 0.32
0.31 0.26
0.31 0.27
0.29 0.32
0.40 0.32
0.40 0.32
0.37 0.30
0.29 0.23
0.32 0.26
Apparent sadness
Reported sadness
Inner tension
Reduced sleep
Reduced appetite
Concentration difficulties
Lassitude
Inability to feel
Pessimistic thought
Suicidal thought


Correlation coefficient
Unadjusted
Adjusted
Panel C
0.35
0.30
0.25
0.20
0.15
0.10
0.5
0
0.31 0.27
0.30 0.26
0.25 0.21
0.24 0.25
0.23 0.26
0.28 0.24
0.27 0.23
0.29 0.25
0.22 0.19
0.24 0.20
Apparent sadness
Reported sadness
Inner tension
Reduced sleep
Reduced appetite
Concentration difficulties
Lassitude
Inability to feel
Pessimistic thought
Suicidal thought

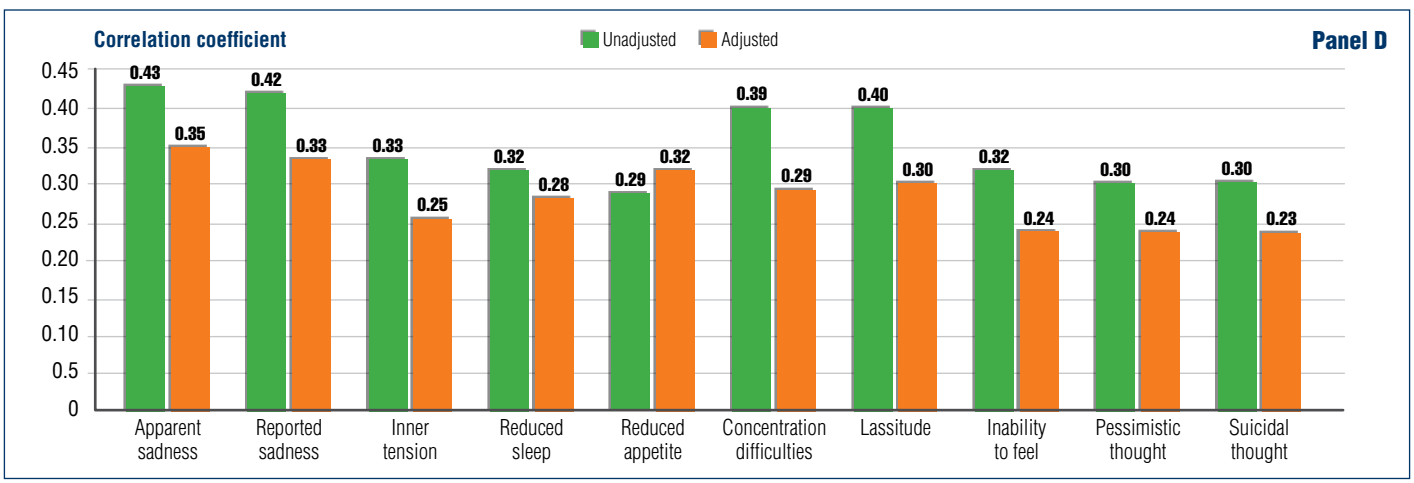

Correlation coefficient
Unadjusted
Adjusted
Panel D
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.5
0
0.43 0.35
0.42 0.33
0.33 0.25
0.32 0.28
0.29 0.32
0.39 0.29
0.40 0.30
0.32 0.24
0.30 0.24
0.30 0.23
Apparent sadness
Reported sadness
Inner tension
Reduced sleep
Reduced appetite
Concentration difficulties
Lassitude
Inability to feel
Pessimistic thought
Suicidal thought

FIGURE 1

(Panel A-D). Unadjusted and Partial Correlations between facets of depression and illness intrusiveness. Bars represent the zero order and partial Spearman's Correlations coefficients estimating the association facets of individual item scores of the MADRS scale and IIRS scores (Panel A: global IIRS scores; Panel B: Instrumental Domain scores; Panel C: Intimacy Domain scores; Panel D: Development Domain scores). Partial correlations have been adjusted for age. sex. education. marital status. having children. employment. primary psychiatric diagnosis. frequency of relapses in the past 10 years. frequency of physical exercise. BMI. number of comorbidities. disease vintage. number of psychotropic medications.

ets of depression are equally contributing to overall lifestyle disruption caused by the disease. It may be surprising that reporting of suicidal thoughts does not seem to provide a major contribution to illness-related interference on daily life. However only few patients in our sample reported such symptom and its overall effect might then be underestimated.

The secondary aim of our study was evaluating socio-demographic and clinical correlates of IIRS. Our data showed that patients reporting more than 2 depressive episodes in the last 10 year had poorer IIRS scores. Treating depression to full symptoms resolution and maintenance of remission is a key endpoint of therapy since the disability related to chronic depression and recurrent pattern of disease is substantial. However. this has been an elusive target of therapy for many patients so far. Adherence issues. inappropriate treatment and late referral to specialized healthcare are often reported as key barriers to successful induction and maintenance of remission among MDD patients [27]. An important finding of our study was that regimen complexity (i.e. number of prescription psychotropic drugs) was strongly associated with illness intrusiveness independent of depression severity. Our results are consistent with a large body of evidence showing that treatment factors are key drivers of HRQOL and life-style interference [22] which in turn might hamper medication adherence [28]. The management of complex regimens require greater organizational accommodations in patients' daily life and need significant self-care abilities [28]; additionally psychotropic drugs are burdened with significant side-effects. and their use may be associated with self-stigma issues [28]. all factors leading to reduced adherence and persistence on treatment for the full course of therapy.

Finally. we did not find any significant interaction between depression severity and IIRS scores across different depressive unipolar diagnosis: our sample size achieved 80% power of detecting a small effect size interaction ($f \geq 0.12$). thus making additional stratified analysis not justified. However. the aim of our study was to evaluate the association between depression severity and Illness intrusiveness independent of the underlying disease. since scores of depression severity scales are often the primary endpoint in RCTs.

This study has several strengths worth mentioning. First. assessment severity relied on clinician-rated scales. which help overcome common method bias. Second. the large sample size allowed us to adjust for several potential confounders. Third. heterogeneity in symptoms severity among our sample let us estimate the relative burden of patients on remission and compare a wide range of symptoms severity.

However. our study has some weaknesses to be taken into account. The cross-sectional design does not allow to draw causal inferences; moreover. the diagnosis of depressive disorders was based on psychiatrists' clinical evaluation carried out during a regular outpatient visit and standardized methods were not uniformly adopted (e.g. Structured Clinical Interview for DSM Disorders; SCID). Consequently we cannot rule out the possibility of classification bias.

Additionally. despite IIRS scale has been extensively used in several chronic conditions worldwide. it has not received formal validation in the Italian psychiatric population. The Italian version of the IIRS has been used in 3 previous published studies with patients suffering from chronic and autoimmune diseases [29-31]: IIRS scale was translated by professional translators. and back-translation was carried-out to corroborate the validity of the process. Although cross-cultural validation studies have generally demonstrated excellent reliability and criterion validity of the total IIRS score. the trans-national stability of the Intimacy subscale has been questioned in French and Asian studies [14]. Hence. results pertaining this subscale should be interpreted cautiously.

Finally. we cannot discount the possibility that selection bias occurred. In order to capture potentially important regional variation. we selected centers located in each Italian region. operating both in university and community hospitals. with both large and relatively small catchment area: however. we could not evaluate the reasons for two cases of non-participation nor we could estimate the attrition rate for the

study. Therefore. our results may not be fully generizable to the Italian population of patients with major depressive disorders seeking care in outpatient mental health services.

Conclusion

We demonstrated wide differences in life-style disruption across depression severity classes. suggesting that the potential quality of life improvement achievable with appropriate therapy is substantial. However we showed that residual impairment due to illness intrusiveness might persist among patients on clinical remission. Additionally we showed that treatment related issues such as the excessive regimen complexity often required to treat the multifaceted manifestations of the disease. might be associated with substantial life-interference irrespective of symptoms severity. Since increased treatment-related illness intrusiveness might lead to poor adherence. the symptom-reducing potential of any additional medication should be carefully considered by clinicians vis-à-vis the risk for increased therapy burden and its impact on quality of life.

Acknowledgement & Authors' Contribution
The conduct of this study has been funded by DoxaPharma s.r.l. The investigators had full access to the data and vouch for data integrity. FA and NL contributed equally to this work. NL contributed to study concept development. study design. data interpretation. manuscript drafting. performed data analysis and approved the final version of the manuscript. FA contributed to data interpretation. drafted the first version of the manuscript. and approved the final version of the manuscript. BA. VM. MC contributed to study concept development. study design. data interpretation. supervised the scientific conduct of the study and approved the final version of the manuscript. Members of the ILDE Study Group design. data interpretation and approved the final version of the manuscript.

Take home messages for psychiatric care

- Depression is a primary determinant of years lost due to disability and exerts a detrimental impact on functional impairment and quality of life. However. the relationship between the severity of depressive symptoms and illness intrusiveness is still scarcely characterized
- We demonstrated a strong graded association between depression severity and life-style disruption in all dimensions tapped by the Illness Intrusiveness Rating Scale (IIRS)
- All facets of depression are equally contributing to overall lifestyle disruption caused by the disease
- Patients with severe symptoms showed the highest IIRS score compared to any other chronic condition investigated so far. A residual impairment persists even after partial or complete clinical recovery
- The potential quality of life improvement achievable with appropriate therapy is substantial
- Polypharmacy strongly contributes to life domains' disruption. thus suggesting further efforts to reduce regimen complexity

References

1 DeSalvo KB. Bloser N. Reynolds K. et al. *Mortality prediction with a single general self-rated health question: a meta-analysis*. J Gen Intern Med 2006;21:267-75.
2 Dowd JB. Zajacova A. *Does the predictive power of self-rated health for subsequent mortality risk vary by socio-economic status in the US?* Int J Epidemiol 2007;36:1214-21.
3 Neri L. Brancaccio D. Rocca Rey LA. et al. *Social support from health care providers is associated with reduced illness intrusiveness in hemodialysis patients*. Clin Nephrol 2010;75:125-34.
4 World Health Organization (WHO). *The Global Burden of Disease: 2004 Update*. Geneva: WHO 2008.
5 Rapaport MH. Clary C. Fayyad R. et al. *Quality-of-life impairment in depressive and anxiety disorders.* Am J Psychiatry 2005;162:1171-1178.
6 Pyne JM. Patterson TL. Kaplan RM. et al. *Preliminary longitudinal assessment of quality of life in patients with major depression*. Psychopharmacol Bull 1997;33:23-29.
7 Hays RD. Wells KB. Sherbourne CD. et al. *Functioning and well-being outcomes of patients with depression compared with chronic general medical illnesses*. Arch Gen Psychiatry 1995;52:11-9.
8 Schonfeld WH. Verboncoeur C J. Fifer SK. et al. *The functioning and well-being of patients with unrecognized anxiety disorders and major depressive disorder.* J Affect Disord 1997;43:105-19.
9 Daly EJ. Trivedi MH. Wisniewski SR. et al. *Health-related quality of life in depression: a STAR*D report.* Ann Clin Psychiatry 2010;22:43-55.
10 Hirschfeld RMA. Dunner DL. Keitner G. et al. *Psychosocial functioning improve independent of depressive symptoms? A comparison of nefazodone. psychotherapy. and their combination*. Biol Psychiatry R 2002;51:123-33.
11 Montgomery SA. Asberg M. *A new depression scale designed to be sensitive to change*. Br J Psychiatry 1979;134:382-9.
12 Davidson J. Turnbull CD. Strickland R. et al. *The Montgomery-Asberg Depression Scale: reliability and validity*. Acta Psychiatr Scand 1986;73: 544-8.

[13] Parker RD. Elizabeth P. Flint HB. et al. *A three-factor analytic model of the MADRS in geriatric depression*. Int J Geriatr Psychiatry 2003;18: 73-77.

[14] Devins GM. *Using the illness intrusiveness ratings scale to understand health-related quality of life in chronic disease*. J Psychosom Res 2010;68:591-602.

[15] International Labour Organization (ILO). *Resolution concerning the International Classification of Status in Employment (ICSE) adopted by the Fifteenth International Conference of Labour Statisticians. 1993*. http://www.ilo.org/global/statistics-and-databases/statistics-overview-and-topics/status-in-employment/current-guidelines/lang--en/index.htm.

[16] Shawaryn MA. Schiaffino KM. LaRocca NG. et al. *Determinants of health-related quality of life in multiple sclerosis: the role of illness intrusiveness*. Multiple Sclerosis 2002;8:310-8.

[17] Franche R. Abbey S. Irvine J. et al. *Sex differences in predictors of illness intrusiveness 1 year after a cardiac event*. J Psychosom Res 2004;56:125-132.

[18] Abram HS. Moore GL. Westervelt FB. *Suicidal behavior in chronic dialysis patients*. Am J Psychiatry 1971;127:1199-204.

[19] Hong BA. Smith MD. Robson AM. et al. *Depressive symptomatology and treatment in patients with end-stage renal disease*. Psychol Med 1987;17:185-90.

[20] Devins GM. *Illness intrusiveness and the psychosocial impact of lifestyle disruptions in chronic life-threatening disease*. Adv Ren Replace Ther 1994;1:251-63.

[21] Robb JC. Cooke RG. Devins GM. et al. *Quality of life and lifestyle disruption in euthymic bipolar disorder*. J. Psychiat. Res 1997;31:509-517.

[22] Devins GM. *Using the illness intrusiveness ratings scale to understand health-related quality of life in chronic disease*. J Psychosom Res 2010;68:591-602.

[23] Kessing LV. *Cognitive impairment in the euthymic phase of affective disorder*. Psychol Med 1998;28:1027-38.

[24] Smith DJ. Muir WJ. Blackwood DHR. *Neurocognitive impairment in euthymic young adults with bipolar spectrum disorder and recurrent major depressive disorder*. Bipolar Disord 2006;8:40-6.

[25] Paradiso S. Lamberty GJ. Garvey MJ. et al. Cognitive impairment in the euthymic phase of chronic unipolar depression. J Nerv Ment Dis1997;185:748-54.

[26] Hammar A. Lundb A. Hugdahla K. *Long-lasting cognitive impairment in unipolar major depression: a 6-month follow-up study*. Psychiatry Res 2003;118:189-96.

[27] Schwenk TL. Evans DL. Laden SK. et al. *Treatment outcome and physician-patient communication in primary care patients with chronic. recurrent depression.* Am J Psychiatry 2004;161:1892-901.

[28] Neri L. Martini A. Andreucci VE. et al. *Regimen complexity and prescription adherence in dialysis patients*. Am J Nephrol 2011;34:71-6.

[29] Fattori A. Neri L. Aguglia E. et al. *Estimating the impact of workplace bullying: humanistic and economic burden among workers with chronic medical conditions*. BioMed Res Int 2015;2015:708908.

[30] Dukes JL. Seelam S. Lentine KL. et al. *Health-related quality of life in kidney transplant patients with diabetes. Clin Transplant* 2013;27:5:E554-62.

[31] Neri L. Brancaccio D. Rocca Rey LA. et al. *Social support from health care providers is associated with reduced illness intrusiveness in hemodialysis patients*. Clin Nephrol 2011;75:125-34.

Appendix I

Centers participating in the Improving Life for DEpression (ILDE) Study Group

Aguglia E[1]. Bellomo A[2]. Bisogno A[3]. Carpiniello B[4]. Cassin A[5]. De Fazio P[6]. Di Sciascio G[7]. Favaretto G[8]. Fraticelli C[9]. Maniscalco T[10]. Marchesi C[11, 12]. Mauri M[13]. Mencacci C[14]. Polselli G[15]. Quartesan R[16]. Risso F[17]. Sciaretta A[18]. Vaggi M[19]. Vender S[20]

1 Department of Psychiatry. University of Catania. 95131 Catania. Italy
2 Department of Clinical and Experimental Medicine. University of Foggia. 71121 Foggia. Italy
3 Department of Mental Health. UO Cava de' Tirreni. 84013 Salerno. Italy
4 Department of Public Health. Clinical and Molecular Medicine. University of Cagliari. 09124 Cagliari. Italy
5 Department of Mental Health. ASS n. 6. 33170 Pordenone. Italy
6 Department of Health Sciences. School of Specialization in Psychiatry. Magna Græcia University of Catanzaro. 88100 Catanzaro. Italy
7 Psychiatric Neuroscience Group. Department of Neurological and Psychiatric Sciences. University of Bari. 70125 Bari. Italy
8 Department of Mental Health. ULSS 7. Conegliano. 31015 Treviso. Italy
9 Unit of Psychiatry. Sant'Anna Hospital. 22100 Como. Italy
10 Department of Mental Health. AULSS Legnago Hospital. Legnago. 37045 Verona. Italy
11 Department of Neuroscience. Psychiatry Unit. University of Parma. 43121 Parma. Italy
12 Mental Health Department. AUSL. 43126 Parma. Italy
13 Department of Experimental and Clinic Medicine. Section of Psychiatry. University of Pisa. 56100 Pisa. Italy
14 Depression Unit. Neuroscience Department. Fatebenefratelli Hospital. 20137 Milan. Italy
15 Department of Neurology and Psychiatry. Policlinico Umberto I. Sapienza University of Rome. 00185 Rome. Italy
16 Division of Psychiatry. Clinical Psychology and Psychiatric Rehabilitation. Department of Medicine. New Faculty of Medicine. University of Perugia. Sant'Andrea delle Fratte. 06156 Perugia. Italy
17 Unit of Psychiatry. A.S.L. CN1. 12100 Cuneo. Italy
18 Servizio Psichiatrico di Diagnosi e Cura (SPDC). Tivoli Hospital. 00019 Rome. Italy
19 Department of Mental Health. ASL3. 16125 Genoa. Italy
20 Department of Clinical and Experimental Medicine. Psychiatry. Faculty of Medicine and Surgery. University of Insubria. 21100 Varese. Italy

ANTIPSYCHOTICS IN TREATMENT-RESISTANT OBSESSIVE-COMPULSIVE DISORDER: WHICH ANTIPSYCHOTIC, WHICH DOSE AND HOW LONG ANTIPSYCHOTIC ADDITION SHOULD BE MAINTAINED

Umberto Albert, Gabriele Di Salvo, Francesca Solia, Giuseppe Maina

Rita Levi Montalcini Department of Neuroscience, University of Turin, Italy; AOU San Luigi Gonzaga of Orbassano, Turin, Italy

Abstract

Objectives: Treatment-resistant Obsessive-Compulsive Disorder (OCD) patients are defined as those who undergo adequate trials of first-line therapies without achieving a satisfactory response. First line treatments for OCD include both serotonin reuptake inhibitors (SRIs) and cognitive behavior therapy (CBT). Because of the high number of OCD patients not responding to first-line treatments (40-60%) and considering the even greater prevalence rate of residual symptoms and significant impairment shown in patients previously described as "clinical responders", the question of the proper treatment of resistant OCD is a clinically meaningful and a practical issue for psychiatrists. Antipsychotic augmentation proved to be an effective strategy for resistant OCD. However, there are unresolved questions concerning which antipsychotic is effective (or more effective) and how antipsychotics should be used in terms of doses and duration of treatment. The purpose of this study is to systematically review available studies on antipsychotic augmentation for treatment-resistant OCD, in order to guide the practical choice.

Materials and methods: We searched on PubMed, Psychnet and Cochrane Libraries from inception to January 2016. Articles published in English and related to the use of antipsychotics in OCD were considered. We evaluated meta-analyses, systematic reviews and randomized controlled trials of adult patients with treatment-resistant OCD.

Results: Antipsychotic augmentation is an evidence-based option for treatment-resistant OCD, with a response rate of approximately 50% within the first 4-to-6 weeks. Aripiprazole (10-15 mg/day) and risperidone (0.5-2 mg/day) are effective, olanzapine (10 mg/day) is possibly effective. Haloperidol addition is also a viable option, particularly in patients with comorbid tic disorders. Given results of studies performed to date quetiapine should be regarded as non-effective. Preliminary results from open label studies suggest that antipsychotic augmentation, once effective, should be maintained in order to maintain remission.

Conclusions: Not all antipsychotics are effective as add-on treatments in resistant OCD. Characteristics of patients and side effects generally associated with each different antipsychotic may guide the practical choice. Further research is required concerning the comparative effectiveness among antipsychotics, the optimal target dose and the ideal duration of antipsychotic addition. In our opinion, antipsychotic augmentation in patients who responded to this treatment should be maintained in order to prevent relapses. However, clinicians must remember patients' exposure to the common and serious adverse effects associated with long-term antipsychotic administration, especially metabolic disturbances.

Key words: Obsessive-Compulsive Disorder (OCD), antipsychotic, augmentation, treatment, treatment-resistant OCD

Correspondence

Umberto Albert
umberto.albert@unito.it

Introduction

Obsessive-compulsive disorder (OCD) is a heterogeneous psychiatric illness with a lifetime prevalence in the general population of approximately 2-3%, making it a far more common disorder than previously believed [1]. The diagnosis is made by the presence of recurrent or persistent, upsetting thoughts, images, or urges, which are experienced as intrusive and unwanted (obsessions), and excessive repetitive behaviors or mental acts performed in response to these obsessions (compulsions) [2].

First line treatments for OCD include both serotonin reuptake inhibitors (SRIs) (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and clomipramine), and cognitive behavior therapy (CBT) – in the forms of exposure and response prevention (ERP) and/or cognitive restructuring [3-11]. Both the above-mentioned pharmacological and psychological approaches have been recognized more effective than wait-list, inactive psychological treatments or placebo in individual randomized controlled trials (RCT) [12-15]. The severity of the disorder (in terms of severity of obsessive-compulsive symptoms or the severity of the associated depressive symptomatology) and the age of the patient might guide clinicians in the choice of the first approach: for an adult patient affected by a severe OCD, pharmacotherapy with an SSRI is generally considered a correct first-line approach. Analyzing the relative efficacy between different SRIs, no significant difference could be identified between citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, according to a Cochrane review depicting 17 RCTs [16]. Equally, the SSRI escitalopram improved OCD symptoms without any significant difference as compared to paroxetine [17]. Nevertheless, 40-60% of OCD patients do not respond satisfactorily to the initial SRI monotherapy [18-20]. Additionally, those patients who are defined as "clinical responders" according to stringent response criteria (i.e., typically a greater than 25 or 35% decline in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) rating) often fail to show later on a complete remission of their symptoms and/or continue to experience significant impairment from their residual symptoms in terms of reduced quality of life [21].

Because of the high number of OCD patients not responding to first-line treatments, the question of the proper treatment of resistant OCD is a clinically meaningful and practical issue for psychiatrists.

Definition of and practical steps to be implemented for treatment-resistant OCD

Patients who undergo adequate trials of first-line therapies without achieving a satisfactory response are defined as treatment-resistant OCD patients. Clinical response is usually defined as a reduction in the Y-BOCS score ≥ 35% or ≥ 25% with respect to baseline [22]. More specifically, stages of response to treatment have been recently proposed, according to an international expert consensus: treatment response is defined as 35% or greater reduction of Y-BOCS and Clinical Global Impression (CGI) 1 or 2; partial response as greater than 25% but less 35% Y-BOCS reduction and CGI at least 3; non response as less than 25% Y-BOCS reduction and CGI 4. Furthermore, remission is achieved if the person no longer meets syndromal criteria for the disorder and has no more than minimal symptoms (Y-BOCS ≤ 12) and CGI 1 or 2 for at least one week; recovery is obtained if the person no longer meets syndromal criteria for the disorder and has no more than minimal symptoms (Y-BOCS ≤ 12) and CGI 1 or 2 for at least one year [23].

Practically, several issues must be considered and questions have to be addressed, before confirming a condition of treatment-resistance of OCD:

1. clinicians should correctly make the diagnosis of OCD. Particularly, other symptoms should not be inappropriately considered as obsessions or compulsions (obsessive-compulsive personality disorder; ruminations occurring in major depressive disorder or other anxiety disorders; repetitive stereotyped behaviors encountered in psychoses, in mental retardation or in organic mental disorders; obsessive concerns about body shape or ritualized eating behaviors in eating disorders; patterns of behaviors, interests or restricted and repetitive activities in autism);
2. clinicians should check that the patient has been exposed to an adequate pharmacological trial (SRIs) in terms of appropriate doses and for at least 12 weeks. Guidelines provide minimum target and maximum doses to be used in OCD (see for example those of the APA Guidelines, illustrated in Table I); a meta-analysis confirmed that moderate-high dosages are more effective in treating OCD and thus should be prescribed before defining a patient as resistant [24];
3. the potential presence of medical or psychiatric comorbidities that could affect treatment response should be assessed (e.g., paradigmatic the case of OCD comorbid with bipolar disorder, where treatment with high doses of SRIs could worsen

Table I. Doses of serotonin reuptake inhibitors (SRIs) in the treatment of obsessive-compulsive disorder according to American Psychiatry Association guidelines (2007) [7].

Compound SRI	Starting dose and incremental dose (mg/day)*	Usual target dose (mg/day)	Usual maximum dose (mg/day)	Occasionally prescribed maximum dose (mg/day)†
Citalopram	20	40-60	80	120
Clomipramine	25	100-250	250	__ ‡
Escitalopram	10	20	40	60
Fluoxetine	20	40-60	80	120
Fluvoxamine	50	200	300	450
Paroxetine	20	40-60	60	100
Sertraline §	50	200	200	400

* Some patients may need to start at half this dose or less to minimize undesired side effects such as nausea or to accomodate anxiety about taking medications; † These doses are sometimes used for rapid metabolizers or for patients with no or mild side effects and inadeguate therapeutic response after 8 weeks or more at the usual maximum dose; ‡ Combined plasma levels of clomipramine plus desmethylclomipramine 12 hours after the dose should be kept below 500 mg/mL to minimize risk of seizures and cardiac conduction delay; § Sertraline, along among the selective serotonin reuptake inhibitors, is better absorbed with food.

both bipolar disorder – mixed episodes, rapid cycling, switch – and OCD) [25 26];

4. clinicians may also keep in mind that the first available strategy could be just waiting for the treatment to produce a full response, since some individuals who fail to improve after three months of treatment at adequate doses may turn into treatment responders after additional months of continued treatment. This strategy, however, should be strictly reserved to patients who showed at least a partial response during the initial months of treatment [27 28];
5. finally, psychoeducational interventions directed to the families might help to establish a therapeutic alliance, to provide education about the disorder and its treatment, to improve family problem solving skills, and to ameliorate compliance to drug treatments [29-31]. Indeed, the family may have a potential role in reinforcing the disorder and reducing patient compliance. Family members tend to become emotionally over-involved, neglecting their own needs and at the same time perpetuating the cycle of obsessions and compulsions. On the other hand, family members might express criticism by voicing expectations that the patient "just snaps out of it". Both attitudes, besides worsening relatives' quality of life [32 33], contribute to the maintenance of patient's symptoms as well [34].

Antipsychotic augmentation in treatment-resistant OCD

Several therapeutic options are available for treatment resistant OCD; however, only two strategies are considered, to date, evidence-based treatments for resistant OCD based on placebo-controlled randomized trials: antipsychotic augmentation of SRIs and cognitive-behavior therapy addition. This latter option proved to be effective in several open-label studies (see for an example of its use in a naturalistic setting resembling that of a clinical practice the study by Albert et al.) [35] and at least one well-performed controlled (stress management training as the inactive/placebo psychological treatment arm) randomized trial [36].

Antipsychotic augmentation of SRIs is an evidence-based treatment for resistant OCD; its efficacy has been confirmed by several randomized, double-blind and placebo-controlled trials and by several meta-analyses.

Atypical antipsychotic medications are approved only for the treatment of Schizophrenia, Bipolar Disorder and Major Depression under drug-specific circumstances. However, their use is rapidly increasing and their off-label prescription is, at least partially, responsible for their widespread use [37-41]. It has been estimated that, among adults, off-label prescriptions represent 40 to 75% of all antipsychotic prescriptions [41].

Antipsychotic drugs are generally recommended as a class for several diagnoses including treatment-resistant OCD, although they are not all the same in their efficacy, reflecting the differences in pharmacokinetic and pharmacodynamic profiles of each drug. In fact, there are still some unresolved questions concerning which atypical antipsychotic could be more effective as an evidence-based treatment for treatment-resistant OCD. Moreover, no advice is provided on how to use a specific antipsychotic for this specific disorder, in terms of doses and duration of treatment.

The purpose of this paper is to systematically review available studies on antipsychotic augmentation for treatment-resistant OCD, focusing on efficacy and comparative effectiveness (where possible) of antip-

sychotics, in order to provide a guidance for clinicians on which antipsychotic (and at which dose) should be preferred in resistant OCD.

Materials and methods

We searched on PubMed, Psychnet and Cochrane Libraries from inception to January 2016. Articles published in English and related to the use of antipsychotics in OCD were evaluated. The keyword "antipsychotic" was combined using the boolean AND with "obsessive-compulsive disorder". An additional search was performed combining OCD with "aripiprazole", "olanzapine", "quetiapine", "paliperidone", "risperidone", "ziprasidone" via the Boolean AND. Finally, a manual search for reference lists from articles selected in the previous search and for any relevant reviews was done. Search results were limited to open-label trials and randomized controlled trials of adult patients with treatment resistant OCD.

Results

Is antipsychotic augmentation an evidence-based treatment for resistant OCD?

The use of antipsychotic addition to SRIs in resistant OCD is supported by several randomized, double-blind, placebo-controlled studies; review and meta-analytical studies also confirm that augmentation of SRIs with antipsychotic drugs can be considered a valid treatment option in resistant OCD [42-52].

In summary, the evidence based on the meta-analytic calculations suggests an efficacy of this pharmacological strategy measured by both the response rates (criterion: Y-BOCS reduction ≥ 35%) and the changes in Y-BOCS total score; Dold et al. calculated an overall response rate to antipsychotic addition (all RCTs, including those where antipsychotics proved to be ineffective) of approximately 30% [52]; however, studies in which the active compound (antipsychotic) differentiated from placebo (positive studies) found response rates around 50% [43]. When response to antipsychotic addition occurs, it is evident within the first 4-6 weeks [43 50]. According to these results, it may be advisable to change strategy when antipsychotic addition after 6 weeks results ineffective. However, not all antipsychotics have been studied in double-blind conditions and differences in efficacy exist between antipsychotics.

Which antipsychotics proved effective in resistant OCD in double-blind, placebo-controlled studies?

Efficacy: first generation antipsychotics

Two studies investigated augmentation of SRIs with typical antipsychotics (haloperidol and pimozide) [53 54]; only haloperidol proved to be effective in a double-blind, placebo-controlled study, particularly in patients with comorbid tic disorders [54 55]. However, the side effect profile of haloperidol, with dose-dependent extrapyramidal symptoms, limits the potential benefit

Table II. Efficacy of antipsychotic augmentation in treatment-resistant OCD: double-blind, placebo-controlled studies.

Antipsychotic	Authors	Sample (N)	Trial duration (weeks)
Aripiprazole	Muscatello et al., 2011 [66] Sayyah et al., 2012 [67]	40 39	16 12
Haloperidol	McDougle et al., 1994 [54]	34	4
Olanzapine	Bystritsky et al., 2004 [68] Shapira et al., 2004 [69]	26 44	6 6
Paliperidone	Storch et al., 2013 [70]	34	8
Quetiapine	Atmaca et al., 2002 *[57] Denys et al., 2004 [58] Carey et al., 2005 [59] Fineberg et al., 2005 [81] Kordon et al., 2008 [60] Diniz et al., 2011 #[61]	27 40 42 21 40 54	8 8 6 16 12 12
Risperidone	McDougle et al., 2000 [62] Hollander et al., 2003 [63] Erzegovesi et al., 2005 [64] Simpson et al., 2013 [65]	36 16 20 60	6 8 6 8

* Single-blind, placebo-controlled study; # Double-blind placebo and clomipramine controlled study.

of this strategy; by comparison, the atypical antipsychotics are associated with fewer extrapyramidal symptoms, though they are known to be associated with a higher risk of metabolic adverse effects [56].

Efficacy: second generation/atypical antipsychotics

Concerning the efficacy of second-generation antipsychotic augmentation of SRIs in treatment-resistant OCD, there are six RCTs regarding the addition of quetiapine [57-61 81], four risperidone [62-65], two aripiprazole [66 67], two olanzapine [68 69] and one paliperidone [70]. Results of double-blind, placebo-controlled studies (together with doses used in each study) are summarized in Table II.

Aripiprazole and risperidone both differentiated from placebo in all studies and may be considered effective. No evidence could be identified for the efficacy of adjunctive quetiapine (no difference in response between quetiapine and placebo in four of the five double-blind studies) and olanzapine (one positive study [68] and one negative [69]). However, the negative study with olanzapine [69] was biased by the fact that the Authors included patients not responding to only 8 weeks of SRI monotherapy; thus patients in both the placebo and the olanzapine arms showed a significant response rate. Our single-blind study comparing olanzapine with risperidone addition showed similar response rates to both compounds, suggesting equivalent efficacy [71]. We then think that olanzapine may be a valid alternative to aripiprazole and risperidone as an augmentation strategy in resistant patients. The paliperidone negative study [70] suffered from the same bias: treatment resistance was defined as an entry YBOCS total score of 19 or greater despite at least two adequate SRI monotherapy trials, one of which included the SRI currently being taken by the patient provided that the duration of treatment was only 8 weeks at a medium-to-high dose. Paliperidone did not differentiate from placebo: paliperidone administration resulted in significant baseline to post-treatment reductions in obsessive-compulsive symptoms (-7.98 points in YBOCS score), and placebo administration also resulted in medium size, trend-level significant YBOCS changes (-4.02 points). Our conclusion is that paliperidone may have a potential efficacy in treating OCD patients resistant to SRIs, although further studies are needed. Future studies might benefit from including patients whose resistance to treatments is prospectively evaluated in a trial lasting a minimum of 12 weeks at the maximum dose.

Comparative effectiveness

Concerning comparative effectiveness of antipsychotics in OCD, we could retrieve only four studies [71-74]. Results of these studies are summarized in Table III. The first one compared risperidone and haloperidol addition with a crossover design: each patient received a 2-week trial of adjunctive risperidone, haloperidol and placebo [72]; both risperidone and haloperidol significantly reduced obsessions

Dose (mg/die)	Mean dose (mg/die)	Minimal length of SRI treatment before enrollment in the study	Results
15 (fixed-dose) 10 (fixed-dose)	15 (fixed-dose) 10 (fixed-dose)	12 12	Aripiprazole > Placebo Aripiprazole > Placebo
2-10	6.2 ± 3.0	12	Haloperidol > Placebo
5-20 5-10	11.2 ± 6.5 6.1 ± 2.1	12 8	Olanzapine > Placebo Olanzapine = Plabebo (patients in both arms improved)
3-9	4.94	8	Paliperidone = Placebo (patients in both arms improved)
50-200 100-300 25-300 50-400 400-600 50-200	91 ± 41 200 168.8 ± 120.8 215 ± 124 - 142 ± 65	12 8 12 12 12 8	Quetiapine > Placebo Quetiapine > Placebo Quetiapine = Placebo Quetiapine = Placebo Quetiapine = Placebo Quetiapine < Placebo
1-6 0.5-3 0.5 (fixed-dose) 0.25-4	2.2 ± 0.7 2.25 ± 0.86 0.5 (fixed-dose) 1.9 ± 1.1	12 12 12 12	Risperidone > Placebo Risperidone > Placebo Risperidone > Placebo Risperidone > Placebo

Table III. Comparative efficacy of antipsychotic augmentation in treatment-resistant OCD.

Authors	Study design	Antipsychotics	Sample (N)
Li et al., 2005 [72]	Double-blind	Risperidone *vs* Haloperidol	16
Maina et al., 2008 [71]	Single-blind	Risperidone *vs* Olanzapine	50
Selvi et al., 2011 [73]	Single-blind	Risperidone *vs* Aripiprazole	41
Shoja Shafti et al., 2015 [74]	Double-blind	Aripiprazole *vs* Quetiapine	44

Hal: Haloperidol; Risp: Risperidone.

when compared with placebo, and there was a tendency for haloperidol, and to a lesser degree for risperidone, of reducing compulsion and YBOCS total score. However, 40% of patients terminated haloperidol treatment early owing to intolerable side effects, versus none in the risperidone phase. Maina and colleagues (2008) directly compared, in a single-blind study, risperidone and olanzapine addition to SRIs in resistant OCD patients: the two compounds resulted equally effective in improving obsessive-compulsive symptoms [71]. Selvi and coworkers (2011), in a single-blind study, compared aripiprazole and risperidone augmentation: both drugs proved to be effective strategies in resistant patients, although a significantly higher response rate was found with risperidone (72.2%) compared to aripiprazole (50%) [73]. Shoja Shafti and Kaviani (2015), finally, compared in a double-blind study the efficacy and safety of aripiprazole versus quetiapine. They found a statistically significant difference in response rates with quetiapine (54.5%) compared to aripiprazole (27.3%) [74].

Which antipsychotic dose should be used?

Dose ranges of antipsychotics and mean final doses used in double-blind studies on antipsychotic addition in resistant OCD are reported in Table II. Concerning antipsychotics that differentiated from placebo, aripiprazole appeared effective at a dose of 10 and 15 mg/day, olanzapine at a mean dose of 11 mg/day, risperidone at a dose comprised between 0.5 and 2 mg/day. Haloperidol proved effective at a mean final dose of 6 mg/day, but with significant side effects.

How long antipsychotic addition should be maintained?

Trial duration of double-blind studies on antipsychotic augmentation in treatment-resistant OCD (Tab. II) has been comprised between 6 and 12 weeks, with the exceptions of 4 weeks in the haloperidol study [54] and 16 weeks in the aripiprazole one [66]. We could not find double-blind maintenance studies on antipsychotic augmentation in OCD.

A recent single-blind study compared risperidone to CBT augmentation during a six-month maintenance phase. Foa and colleagues (2015) followed-up 40 patients with resistant OCD who responded (Y-BOCS decrease ≥ 25%) to 8-week adjunctive risperidone or CBT (single-blind, placebo-controlled acute study) [65]; responders continued the augmentation strategy they received acutely over further six months. Response was maintained in both groups. Since CBT patients improved more during acute treatment than risperidone patients, CBT yielded superior outcomes six months later [75]. Nevertheless, since risperidone preserved his efficacy, this study may support the need of sustaining antipsychotic augmentation in patients who acutely responded to this treatment.

However, exactly how long adjunctive antipsychotic treatment should be maintained remains an unanswered question. Only a study examined relapse rates after antipsychotic discontinuation; this study showed that the discontinuation of the antipsychotic in patients previously responsive only to the augmentation strategy leads to an exacerbation of obsessive-compulsive symptoms (relapse) in the vast majority of patients (83.3% within the 24-week follow-up); 72.2% of patients relapsed within the first 8 weeks from discontinuation [76]. Although retrospective, this study provides additional evidence that antipsychotic augmentation has to be maintained for patients who respond to this strategy.

Discussion and Conclusions

The purpose of this paper was to systematically review available studies on antipsychotic augmentation

Trial duration (weeks)	Dose (mg/die)	Minimal length of SRI treatment before enrollment in the study	Results
2	Risperidone: 1 Haloperidol: 2	2	Obsessions: Hal = Risp > Placebo Compulsions: Hal = Risp = Placebo Total YBOCS: Hal > Risp = Placebo
8	Risperidone: 1-3 Olanzapine: 2.5-10	16	Risperidone = Olanzapine
8	Risperidone: 3 Aripiprazole: 15	12	Risperidone > Aripiprazole
12	Aripiprazole: 10 Quetiapine: 300	12	Quetiapine > Aripiprazole

for treatment-resistant OCD, focusing on efficacy and comparative effectiveness (where possible) of antipsychotics, in order to provide a guidance for clinicians on which antipsychotic (and at which dose) should be preferred in resistant OCD.

The currently available evidence suggests that antipsychotic augmentation of SRIs is an evidence-based treatment option for OCD patients not responding to at least 12 weeks at a medium-to-high SRI dose.

Vulink and colleagues examined the efficacy of the combination of SRIs and antipsychotic from beginning of treatment in non-refractory OCD patients, supporting that the combination of quetiapine (300-450 mg) and citalopram (60 mg) was more effective than citalopram alone in reducing OCD symptoms in treatment-naive or medication-free OCD patients [77]. In our opinion, however, given the adverse effect profile of long-term antipsychotic use and the lack of additional evidence of the efficacy of this combination *ab initio*, antipsychotic augmentation should be reserved for resistant patients. The use of antipsychotics in monotherapy either in drug-naïve or resistant patients has never been studied under double-blind conditions.

Clinicians should expect a response rate of approximately 50% in 4-to-6 weeks after antipsychotic addition, given that the choice of the *right* antipsychotic is restricted to aripiprazole, risperidone, and olanzapine. Our conclusions is supported by two positive double-blind studies for aripiprazole (none negative), four for risperidone (none negative) and one for olanzapine (one negative study, but biased – see results). Haloperidol addition is also a viable option, particularly in patients with comorbid tic disorders. Whether resistant patients with comorbid tic disorders respond better to all antipsychotics is still to be determined, as meta-analytic studies support this conclusion (patients with tics: NNT 2.3 *vs* patients without tics: NNT 5.9) but also say that results are biased by the inclusion of the haloperidol study results [43]. Quetiapine should be regarded as non-effective in OCD, given results of studies performed to date (no difference in response between quetiapine and placebo in four of the five double-blind studies).

Data emerging from comparative studies to guide clinicians in the choice between aripiprazole, olanzapine and risperidone are still preliminary and conclusions can't be drawn; characteristics of patients (e.g. BMI at baseline) and side effects generally associated with each different antipsychotic may guide the practical choice.

The characteristic feature of second-generation antipsychotics is a combination of antagonism at the dopamine-D2 receptor and at the serotonin-5-HT2a receptor. Which receptor-binding, in addition to the serotonin reuptake inhibition induced by SSRIs, primarily causes the therapeutic effects of antipsychotic augmentation in resistant OCD appears to be unclear at the present. Haloperidol and risperidone are characterized by a markedly more potent affinity to the D2-receptor than quetiapine and olanzapine [78]. Because haloperidol and risperidone were superior to quetiapine and olanzapine in the meta-analytic calculations, it may be conjectured that the pharmacological effects in OCD are primarily caused by the D2-receptor blockade of the antipsychotic [47]. A recent metaregression analysis suggested that differences in antipsychotic effectiveness could be due to differences in dopamine binding affinities, with increasing D2 and D3 dopamine receptor binding affinities associated with greater effectiveness (greater YBOCS reduction and higher response rates) [49].

An alternative evidence-based strategy for resistant OCD is CBT addition to pharmacotherapy, when CBT is available [79]. We could find only one acute study which directly compared pharmacological (risperidone) and psychological (intensive CBT) augmentation in adult

patients with resistant OCD [65]. This comparative study suggests that intensive CBT is more effective than risperidone addition to SRIs: response rates were 80% and 23% at week 8, respectively; this randomized clinical study concluded that patients with OCD receiving SRIs who continue to have clinically significant symptoms should be offered CBT before antipsychotics given its superior efficacy and less negative adverse effect profile, although clinician should remember that intensive CBT was offered in that study (15 exposure sessions, daily homework – at least 1 hour of self-directed exposures daily, and between-session telephone check-ins, at least 2 sessions outside the clinic to promote generalization to daily life) [65]. Given the strength of the evidence for antipsychotic addition, we do suggest this option especially in patients who showed a partial but unsatisfactory response.

Further research is still required concerning the optimal target dose of antipsychotic to be prescribed in resistant patients; the available evidence suggests to use the following doses: aripiprazole 10-15 mg/day, olanzapine 10 mg/day, risperidone 0.5-2 mg/day. Haloperidol proved effective at a mean final dose of 6 mg/day, but with significant side effects; in clinical practice we advise to use it, e.g. when tic disorder is comorbid, at lower dosages, and augment up to 6 mg/day if response is not evident at lower dosages. Further research is also still required regarding the ideal duration of add-on treatment, its long tolerability and the evaluation of predictors of response. The available evidence points to the need of maintaining antipsychotic addition over the long-term in order to prevent relapses. On the other hand, however, if such treatment is carried out over the long term, patients are exposed to the common and serious adverse effects associated with long-term antipsychotic administration, especially metabolic ones: increased glucose, triglycerides, abdominal circumference, blood pressure and decreased cholesterol HDL [80]. Patients with OCD on antipsychotic treatment may be particularly at risk for metabolic syndrome and should be carefully monitored for metabolic abnormalities and cardiovascular complications: a recent study of our research group showed that metabolic syndrome was present in 21.2% of a sample of 104 OCD patients; metabolic syndrome was associated with the duration of the exposure (lifetime) to antipsychotics [56]. These results add strength to the indication of restricting the use of antipsychotic augmentation in resistant patients, when CBT is not available or feasible, or is ineffective. We strongly advice not using antipsychotic addition to SRIs in drug-naïve, never treated patient.

Further investigations should also assess which SRIs are the most suitable for an antipsychotic augmentation strategy. Moreover, additional work is required to understand the psychobiological mechanisms underlying the efficacy of antipsychotic addition in resistant OCD.

Take home messages for psychiatric care

- Augmentation of SRIs with antipsychotics is an evidence-based strategy in resistant OCD
- The overall response rate to antipsychotic addition is around 50%
- Among atypical antipsychotics, risperidone and aripiprazole may be considered the most effective in resistant OCD
- Further studies are required on the optimal dose and the ideal duration of antipsychotic add-on treatment

References

1 Ruscio AM, Stein DJ, Chiu WT, et al. *The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication.* Mol Psychiatry 2010;15:53-63.

2 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders - 5th ed.* Washington, DC: American Psychiatric Press 2013.

3 March J, Frances A, Carpenter D, et al.; The Expert Consensus Guidelines Series. *Treatment of obsessive-compulsive disorder.* J Clin Psychiatry 1997;58:2-72.

4 Baldwin DS, Anderson IM, Nutt DJ, et al.; British Association for Psychopharmacology. *Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology.* J Psychopharmacol 2005;19:567-96.

5 Baldwin DS, Anderson IM, Nutt DJ, et al. *Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology.* J Psychopharmacol 2014;28:403-39.

6 Canadian Psychiatric Association. *Clinical practice guidelines. Management of anxiety disorders.* Can J Psychiatry 2006;51:9S-91.

7 American Psychiatric Association. *Practice Guideline for the treatment of patients with obsessive-compulsive disorder.* Arlington, VA: American Psychiatric Association 2007.

8 American Psychiatric Association. *Guideline Watch (March 2013): Practice Guideline for the treatment of patients with obsessive-compulsive disorder.* Arlington, VA: American Psychiatric Association 2013.

9 Bandelow B, Zohar J, Hollander E, et al.; World Federation of Societies of Biological Psychiatry (WFSBP). *Guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders-first revision.* World J Biol Psychiatry 2008;9:248-312.

10 Bandelow B, Sher L, Bunevicius R, et al.; WFSBP Task Force on Mental Disorders in Primary Care; WFSBP Task Force

on Anxiety Disorders, OCD and PTSD. *Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder in primary care.* Int J Psychiatry Clin Pract 2012;16:77-84.

11 Katzman MA, Bleau P, Blier P, et al. *Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders*. BMC Psychiatry 2014;14(Suppl 1):S1.

12 Deacon BJ, Abramowitz JS. *Cognitive and behavioural treatments for anxiety disorders: a review of meta-analytic findings.* J Clin Psychol 2004;60:429-41.

13 Eddy KT, Dutra L, Bradley R, et al. *A multidimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive-compulsive disorder.* Clin Psychol Rev 2004;24:1011-30.

14 Fisher PL, Wells A. *How effective are cognitive and behavioural treatments for obsessive-compulsive disorder? A clinical significance analysis.* Behav Res Ther 2005;43:1543-58.

15 Rodrigues H, Figueira I, Gonçalves R, et al. *CBT for pharmacotherapy non-remitters – a systematic review of a next-step strategy.* J Affect Disord 2011;129:219-28.

16 Soomro GM, Altman D, Rajagopal S, et al. *Selective serotonin re-uptake inhibitors* vs *placebo for obsessive-compulsive disorder (OCD).* Cochrane Database Syst Rev 2008;23:CD001765.

17 Stein DJ, Andersen EW, Tonnoir B, et al. *Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study.* Curr Med Res Opin 2007;23:701-11.

18 Alacron RD, Libb JW, Spitler D. *A predictive study of obsessive compulsive response to clomipramine.* J Psychopharmacol 1993;13:210-3.

19 Ravizza L, Barzega G, Bellino S, et al. *Predictors of drug treatment response in obsessive-compulsive disorder.* J Clin Psychiatry 1995;56:368-73.

20 Erzegovesi S, Cavellini MC, Cavedini P, et al. *Clinical predictors of drug response in obsessive-compulsive disorder.* J Clin Psychopharmacol 2001;21:272-5.

21 Goodman WK, McDougle CJ, Barr LC, et al. *Biological approaches to treatment-resistant obsessive compulsive disorder.* J Clin Psychiatry 1993;54:16-26.

22 Rauch SL, Jenike MA. *Management of treatment-resistant obsessive-compulsive disorder: concepts and strategies.* In: Hollander E, Zohar J, Marazziti D, et al., editors. *Current insights in obsessive-compulsive disorder.* Chichester: John Wiley & Sons Ltd 1994.

23 Mataix-Cols D, Fernandez de la Cruz L, Nordsletten AE, et al. *Towards an international expert consensus for defining treatment response, remission, recovery and relapse in obsessive-compulsive disorder: a Delphi survey.* World Pyschiatry 2016; in press.

24 Bloch MH, McGuire J, Landeros-Weisenberger A, et al. *Meta-analysis of the dose-response relationship of SSRI in obsessive-compulsive disorder.* Mol Psychiatry 2010;15:850-5.

25 Ghaemi SN, Wingo AP, Filkowski MA, et al. *Long-term antidepressant treatment in bipolar disorder: meta-analysis of benefits and risks.* Acta Psychiatr Scand 2008;118:347-56.

26 Salvi V, Fagiolini A, Swartz HA, et al. *The use of antidepressants in bipolar disorder.* J Clin Psychiatry 2008;69:1307-18.

27 De Haan E, van Oppen P, van Balkom AJ, et al. *Prediction of outcome and early vs late improvement in OCD patients treated with cognitive behavior therapy and pharmacotherapy.* Acta Psychiatr Scand 1997;96:354-61.

28 McDonough M, Kennedy N. *Pharmacological management of obsessive-compulsive disorder: a review for clinicians.* Harv Rev Psychiatry 2002;10:127-37.

29 van Noppen B, Steketee G, Pato M. *Group and multifamily behavioral treatments for OCD.* In: Hollander E, Stein D, editors. *Obsessive-compulsive disorder: diagnosis, etiology, treatment*. New York: Marcel Dekker 1997, pp. 331-66.

30 Albert U, Maina G, Saracco P, et al. *Multifamily psychoeducational Intervention (MPI) for obsessive-compulsive study: a pilot study.* Epidemiol Psich Soc 2006;15:70-5.

31 Maina G, Saracco P, Albert U. *Family-focused treatments for obsessive-compulsive disorder.* Clin Neuropsychiatry 2006;3:382-90.

32 Albert U, Salvi V, Saracco P, et al. *Health-related quality of life among first degree relatives of patients with obsessive-compulsive disorder in Italy.* Psychiatry Service 2007;58:970-6.

33 Grover S, Dutt A. *Perceived burden and quality of life of caregivers in obsessive-compulsive disorder.* Psychiatry Clin Neurosci 2011;65:416-22.

34 van Noppen B, Steketee G. *Family response and multifamily behavioral treatment for obsessive-compulsive disorder.* Brief Treat Crisis Interv 2003;3:231-47.

35 Albert U, Aguglia A, Bogetto F, et al. *Effectiveness of cognitive-behavioral therapy addition to pharmacotherapy in resistant obsessive-compulsive disorder: a multicenter study.* Psychother Psychosom 2012;81:383-5.

36 Simpson HB, Foa EB, Liebowitz MR, et al. *A randomized, controlled trial of cognitive-behavioral therapy for augmenting pharmacotherapy in obsessive-compulsive disorder.* Am J Psychiatry 2008;165:621-30.

37 Verdoux H, Tournier M, Bégaud B. *Antipsychotic prescribing trends: a review of pharmaco-epidemiological studies.* Acta Psychiatr Scand 2010;121:4-10.

38 Alexander GC, Gallagher SA, Mascola A, et al. *Increasing off-label use of antipsy-chotic medications in the United States, 1995-2008.* Pharmacoepidemiol Drug Saf 2011;20:177- 84.

39 Comer JS, Mojtabai R, Olfson M. *National trends in the antipsychotic treatment of psychiatric outpatients with anxiety disorders.* Am J Psychiatry 2011;168:1057-65.

40 Gallini A, Donohue JM, Huskamp HA. *Diffusion of antipsychotics in the US And French markets, 1998-2008.* Psychiatr Serv 2013;64:680-7.

41 Carton L, Cottencin O, Lapeyre-Mestre M, et al. *Off-label prescribing of antipsychotics in adults, children and elderly individuals: a systematic review of recent prescription trends.* Curr Pharm Des 2015;21.

42 Sareen J, Kirshner A, Lander M, et al. *Do antipsychotics ameliorate or exacerbate Obsessive Compulsive Disorder symptoms? A systematic review.* J Affect Disord 2004;82:167-74.

43 Bloch MH, Landeros-Weisenberger A, Kelmendi B, et al. *A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder.* Mol Psychiatry 2006;11:622-32.

44 Skapinakis P, Papatheodorou T, Mavreas V. *Antipsychotic augmentation of serotonergic antidepressants in treatment-resistant obsessive-compulsive disorder: a meta-analysis of the randomized controlled trials.* Eur Neuropsychopharmacol 2007;17:79-93.

45 Komossa K, Depping AM, Meyer M, et al. *Second-generation antipsychotics for obsessive compulsive disorder.* Cochrane Database Syst Rev 2010:CD008141.

46 Maher AR, Maglione M, Bagley S, et al. *Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults. A systematic review and meta-analysis.* JAMA 2011;306:1359-69.

47 Dold M, Aigner M, Lanzenberger R, et al. *Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials.* Int J Neuropsychopharmacol 2013;16:557-74.

48 Albert U, De Cori D, Bogetto F, et al. *Treatment-resistant Obses-*

sive-Compulsive Disorder (OCD): focus on antipsychotic augmentation to SRIs. Austin J Psychiatry Behav Sci 2014;1:1023.
[49] Ducasse D, Boyer L, Michel P, et al. *D2 and D3 dopamine receptor affinity predicts effectiveness of antipsychotic drugs in obsessive-compulsive disorders: a metaregression analysis.* Psychopharmacology 2014;231:3765-70.
[50] Veale D, Miles S, Smallcombe N, et al. *Atypical antipsychotic augmenation in SSRI treatment refractory obsessive-compulsive disorder: a systematic review and meta-analysis.* BMC Psychiatry 2014;14:317.
[51] Fineberg NA, Reghunandanan S, Simpson HB, et al. *Obsessive-compulsive disorder (OCD): practical strategies for pharmacological and somatic treatment in adults.* Psychiatry Res 2015;227:114-25.
[52] Dold M, Aigner M, Lanzenberger R, et al. *Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: an update meta-analysis of double-blind, randomized, placebo-controlled trials.* Int J Neuropsychopharmacol 2015;4:18.
[53] McDougle CJ, Goodman WK, Price LH, et al. *Neuroleptic addition in fluvoxamine-refractory obsessive-compulsive disorder.* Am J Psychiatry 1990;147:652-4.
[54] McDougle CJ, Goodman WK, Leckman JF, et al. *Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. A double-blind, placebo-controlled study in patients with and without tics.* Arch Gen Psychiatry 1994;51:302-8
[55] Fineberg NA, Gale TM, Sivakumaran T. *A review of antipsychotics in the treatment of obsessive compulsive disorder.* J Psychopharmacol 2006;21:97-103.
[56] Albert U, Aguglia A, Chiarle A, et al. *Metabolic syndrome and obsessive-compulsive disorder: a naturalistic Italian study.* Gen Hosp Psychiatry 2013;35:154-9.
[57] Atmaca M, Kuloglu M, Tezcan E, et al. *Quetiapine augmentation in patients with treatment resistant obsessive-compulsive disorder: a single-blind, placebo-controlled study.* Int Clin Psychopharmacol 2002;17:115-9.
[58] Denys D, de Geus F, van Megen HJ, et al. *A double-blind, randomized, placebo-controlled trial of quetiapine addition in patients with obsessive-compulsive disorder refractory to serotonin reuptake inhibitors.* J Clin Psychiatry 2004;65:1040-8.
[59] Carey PD, Vythilingum B, Seedat S, et al. *Quetiapine augmentation of SRIs in treatment refractory obsessive-compulsive disorder: a double-blind, randomised, placebo-controlled study.* BMC Psychiatry 2005;5:5.
[60] Kordon A, Wahl K, Koch N, et al. *Quetiapine addition to serotonin reuptake inhibitors in patients with severe obsessive-compulsive disorder: a double-blind, randomized, placebo-controlled study.* J Clin Psychopharmacol 2008;28:550-4.
[61] Diniz JB, Shavitt RG, Fossaluza V, et al. *A double-blind, randomized, controlled trial of fluoxetine plus quetiapine or clomipramine versus fluoxetine plus placebo for obsessive-compulsive disorder.* J Clin Psychopharmacol 2011;31:763-8.
[62] McDougle CJ, Epperson CN, Pelton GH, et al. *A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder.* Arch Gen Psychiatry 2000;57:794-801.
[63] Hollander E, Baldini Rossi N, Sood E, et al. *Risperidone augmentation in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study.* Int J Neuropsychopharmacol 2003;6:397-401.
[64] Erzegovesi S, Guglielmo E, Siliprandi F, et al. *Low-dose risperidone augmentation of fluvoxamine treatment in obsessive-compulsive disorder: a double-blind, placebo-controlled study.* Eur Neuropsychopharmacol 2005;15:69-74.
[65] Simpson HB, Foa EB, Liebowitz MR, et al. *Cognitive-behavioral therapy* vs *risperidone for augmenting serotonin reuptake inhibitors in obsessive-compulsive disorder: a randomized clinical trial.* JAMA Psychiatry 2013;70:1190-9.
[66] Muscatello MR, Bruno A, Pandolfo G, et al. *Effect of aripiprazole augmentation of serotonin reuptake inhibitors or clomipramine in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study.* J Clin Psychopharmacol 2011;31:174-9.
[67] Sayyah M, Sayyah M, Boostani H, et al. *Effects of aripiprazole augmentation in treatment-resistant obsessive-compulsive disorder (a double blind clinical trial).* Depress Anxiety 2012;29:850-4.
[68] Bystritsky A, Ackerman DL, Rosen RM, et al. *Augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder using adjunctive olanzapine: a placebo-controlled trial.* J Clin Psychiatry 2004;65:565-8.
[69] Shapira NA, Ward HE, Mandoki M, et al. *A double-blind, placebo controlled trial of olanzapine addition in fluoxetine-refractory obsessive-compulsive disorder.* Biol Psychiatry 2004;55:553-5.
[70] Storch EA, Goddard AW, Grant JE, et al. *Double-blind, placebo-controlled, pilot trial of paliperidone augmentation in serotonin reuptake inhibitor-resistant obsessive-compulsive disorder.* J Clin Psychiatry 2013;74:527-32.
[71] Maina G, Pessina E, Albert U, et al. *8-week, single-blind, randomized trial comparing risperidone versus olanzapine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder.* Eur Neuropsychopharmacol 2008;18:364-72.
[72] Li X, May RS, Tolbert LC, et al. *Risperidone and haloperidol augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder: a crossover study.* J Clin Psychiatry 2005;66:736-43.
[73] Selvi Y, Atli A, Aydin A, et al. *The comparison of aripiprazole and risperidone augmentation in selective serotonin reuptake inhibitor-refractory obsessive-compulsive disorder: a single-blind, randomised study.* Hum Psychopharmacol 2011;26:51-7.
[74] Shoja Shafti S, Kaviani H. *Aripiprazole* vs *quetiapine in treatment-resistant obsessive-compulsive disorder: a double-blind clinical trial.* Ther Adv Psychopharmacol 2015;5:32-7.
[75] Foa EB, Simpson HB, Rosenfield D, et al. *Six-month outcomes from a randomized trial augmenting serotonin reuptake inhibitors with exposure and response prevention or risperidone in adults with obsessive-compulsive disorder.* J Clin Psychiatry 2015;76:440-6.
[76] Maina G, Albert U, Ziero S, et al. *Antipsychotic augmentation for the treatment-resistant obsessive-compulsive disorder: what if antipsychotic is discontinued?* Int Clin Psychopharmachol 2003;18:23-8.
[77] Vulink NC, Denys D, Fluitman SB, et al. *Quetiapine augments the effect of citalopram in non-refractory obsessive-compulsive disorder: a randomized, double-blind, placebo-controlled study of 76 patients.* J Clin Psychiatry 2009;70:1001-8.
[78] Goddard AW, Shekhar A, Whiteman AF, et al. *Serotonergic mechanisms in the treatment of obsessive-compulsive disorder.* Drug Discov Today 2008;13:325-32.
[79] Albert U, Bogetto F. *Treatment of obsessive-compulsive disorder: drugs, psychotherapy or combined treatments?* Rivista di Psichiatria 2015; in press.
[80] Matsunaga H, Nagata T, Hayashida K, et al. *A long-term trial of the effectiveness and safety of atypical antipsychotic agents in augmenting SSRI-refractory obsessive-compulsive disorder.* J Clin Psychiatry 2009;70:863-8.
[81] Fineberg NA, Sivakumaran T, Roberts A, et al. *Adding quetiapine to SSRI in treatment-resistant obsessive-compulsive disorder: a randomized controlled treatment study.* Int Clin Psychopharmacol 2005;20:223-6.

ITALIAN PSYCHIATRY AND FASCISM: RACIAL LAWS AND LIFE IN PSYCHIATRIC HOSPITALS DURING WORLD WAR II

Valentina Casetti[1 2], **Andreas Conca**[2 3]

[1] Provincia Autonoma di Bolzano; [2] Department of Psychiatry of Bolzano, Italy; [3] Department of childhood and adolescence Psychiatry of Bolzano, Italy

Abstract

Objectives: After the establishment of Mussolini's dictatorship, Italian psychiatry gave a significant contribution to the promotion of eugenics principles and of fascist racism.

Materials and Methods: In 1938 the Italian Society of Psychiatry (SIP), embodied by its president Arturo Donaggio, signed the Manifesto of Racist Scientists.

Results: This document provided scientific justification to the forthcoming Italian racial laws. During World War II patients admitted to psychiatric hospitals suffered from severe deprivations, which caused a 60-fold increased mortality as compared to the general population. However, Italian historiography and the SIP have for long failed to recognize and properly discuss these events.

Conclusions: The authors argue that,in order to prevent further misuse in the future, Italian psychiatry need to gain a full awareness of its history and take responsibilities for the crimes committed. This will allow to achieve a stronger professional integrity and to deal with future ethical challenges in a proper and informed way.

Key words: Fascism, eugenics, racial laws, psychiatry, World War II

Eugenics at the beginning of the 20th century

At the beginning of the 20th century, the emergence of eugenics exerted a significant influence on science worldwide, especially the psychiatric field. The term was coined by Sir Francis Galton to describe a science dealing with the improvement of the "inborn qualities of a race" [1]. Eugenics aimed at preventing the inheritance of undesirable traits or, in its extreme occurrence, at eliminating all individuals considered "unfit". In the late 1920s – early 1930s, eugenics movements were well established in most Western countries, particularly in the US and the UK. The US was the first country to undertake sterilization programs for the purpose of limiting the reproductive rights of the mentally ill. Here, 18.552 individuals were compulsorily sterilized between 1907 and 1940 [2]. In the 1930s, forced sterilization programs were active in various European countries, including Switzerland, Denmark, Estonia, Sweden, and Finland. In Nazi Germany, the application of eugenic principles reached the most destructive forms. Nazi eugenics was influenced by the Swiss psychiatrist Ernst Rüdin (1874-1952). Racial hygiene (*Rassenhygiene*) policies increasingly won favour and advocated the euthanasia of the so-called "life unworth of living" (*Lebensunwertes Leben* [3 4]). The first German compulsory sterilization law was approved in 1933. Between 1934 and May 1945, 360.000 individuals were sterilized [5]; 6.000 (1.7%) of them died during the operation. In 1939, the Aktion T4 programme was initi-

Correspondence

Umberto Albert
umberto.albert@unito.it

ated in an effort to kill all individuals with incurably physical and mental illnesses. Before the programme was discontinued under the pressure of public opinion and the Church, in 1941, 70.000 individuals were killed, including 5.000 children [5 6]. However, the extermination of patients continued in the so-called period of "wild euthanasia". Deliberate killings by starvation and injections undertaken into psychiatric hospitals caused the death of other 100.000 people in 1941-1945 [7]. Overall, the German euthanasia program led to the death of between 250.000 and 300.000 people with physical and mental illnesses [5].

In Italy, eugenics was adapted to the scientific, cultural and institutional contexts and was strongly influenced by Lombroso's theories [8]. The participation of a substantial delegation to The First International Eugenics Congress, held in London in 1912, was a defining moment in the history of Italian eugenics [9]. This event contributed to the organization and institutionalization of the eugenics movement and anticipated the constitution of the first Italian Committee of Eugenic Studies (*Comitato Italiano per gli studi di Eugenica*) (1913). Italian eugenics was opposed to sterilization and killings of people with incurable diseases. Nevertheless, it advocated the use of indirect practices of social prophylaxis, including prevention, education about eugenics, and segregation of dysgenic types. This was also the position of Italian psychiatry [10].

Fascism and Italian psychiatry

The first scientific society for Italian psychiatry, called Italian Phreniatric Society (*Società Freniatrica Italiana* – SFI), was founded in 1873. This name reflected the efforts made by psychiatry to combine itself with organic medicine and neurology while taking distance from psychology. It was changed to Italian Society of Psychiatry (*Società Italiana di Psichiatria* – SIP) in 1932. In 1904 the first comprehensive law on mental health (law 14th February 1904, n. 36) was issued. It described the general principles regulating psychiatric care and established a bond between mental illness and "social dangerousness" [11].

Italian psychiatry and the conditions of mental hospitals and their patients were strongly affected by the establishment of the Fascist dictatorship. In October 1922 Mussolini, who had formed the Fascist Party seven years before, led the March on Rome, which marked the beginning of the Fascist era. Invited by King Emanuele III to form a new government, he became Prime Minister. In 1925 Mussolini declared himself dictator and remained to power until he was deposed in 1943. During Fascism, important state interventions were implemented to centralize, reorganize and modernize social and health sectors; however, the psychiatric sector was excluded from this process [12]. Although 13 new were built, many hospitals remained located in poor-state buildings and the problem of the shortage of beds was not solved [12]. The number of admissions to asylums increased by 30% in 15 years, growing from 60.000 in 1926 to 96.500 in 1941 [13]. Since at that time psychiatric, neurological and psycho-organic diseases were grouped together, patients admitted suffered from a wide range of illnesses, encompassing mental disorders but also dementia, pellagra, epilepsy, tuberculosis, syphilis, alcoholism, and encephalitis [12]. Moreover, the 1930 Penal Code had strengthened the concept of "social dangerousness". This opened the doors of asylums to dissidents and political opponents. Over the 20-year period of Fascisms, 475 antifascists were compulsorily admitted to mental hospitals (a significant number in the asylum of Aversa, near Caserta), often with the consent of their directors. 122 of them died during psychiatric internment [14].

During the 1920s and especially the 1930s, psychiatry progressively supported the fascist ideology. Enrico Morselli (1852-1929), president of the SIF from 1919 to 1929, protected the society from political interferences [15]. At the same time he adhered personally to the Fascist movement and was one of the signatories of the Manifesto of Fascist Intellectuals (*Manifesto degli Intellettuali del Fascismo*). The Manifesto was edited during the Conference of Fascist Culture held in Bologna in 1925. It gathered the signatures of exponents of Italian culture and established the ideological foundation of Fascism. However, the most prominent figure contributing to the promotion of Fascism was Arturo Donaggio (1868-1942), chairman of neurology at the University of Bologna and President of the SIP from 1929 to 1942, who adhered to and fiercely promoted racist ideology. In the XIXth and the first part of the XXth century, racism was embedded in psychiatric knowledge [16]. In Western countries psychiatrists commonly maintained that black people were mentally degenerated because of their "savage" state and of the primitive culture [16]. The fascist imperialist campaign reinforced Italian racism, while the scientific community provided ideological justification to it, although not in such extreme ways as in Germany [17]. While opening the ceremonies of various SIP Congresses held between 1930 and 1940, Donaggio manifested his praise to the regime and

the colonial expansion in Ethiopia; furthermore, he exalted the Italian race and its superiority to black populations [18].

Even more remarkable was the role played by the SIP, embodied by Donaggio, in supporting anti-Jews propaganda. Among European countries, Italian anti-Semitism was probably the least deeply rooted [19]. The Jews represented a small minority (little more than 0.1% of the total population) and were generally well integrated into society; anti-Semitics episodes existed but remained isolated events. In July 1938, *Il Giornale d'Italia* published the Manifesto of Racist Scientists (*Manifesto degli scienziati razzisti*) with the signatures of 10 scientists and scholars, including Donaggio. The Manifesto defined race as a biological concept and announced the existence of a pure "Italian race" of Aryan descent, from which the Jewish one was excluded. Despite lacking a strong scientific rationale, this document provided scientific justification to Italian racism. It combined Italian anti-Semitism, previously almost entirely political or ideological in its nature, with biological theories [20] and paved the way to the forthcoming intensive campaign of anti-Semitism and to the enactment, between September and November 1938, of Italian racial laws. The SIP was the only scientific society to approve the Manifesto [15]. For the Jews in Italy, racial laws resulted in discriminations and restrictions, in being banned from public life and, during the war, in being deported to concentration camps. According to the census of 1938, 58.412 (48.032 Italian and 10.380 foreign) people with at least one Jewish parent were resident in Italy [21]. At the fall of Fascism, in 1943, this number had decreased to around 44.000 [22]. At least 6.000 Jews had emigrated. 6.806, including 612 children, were deported to concentration camps: only 837 people (121 children) survived. 733 other were arrested and, of them, 322 died [23]. In 1939 racial laws were extended to Libya, which was the Italian colony with the greatest number of Jews. The Jewish population was 21.000 in 1911 (when the country was conquered) and 30.387 in 1939 [24]. In Tripoli more than one third of the population were Jewish. After the beginning of the war Italians rigorously upheld the racial laws and adopted more radical policies against the Jews. After Cyrenaica was invaded by Britain and re-conquered by the Italian army in 1941, Italian authorities decided to punish Libyan Jews for the enthusiasm they had expressed with British occupiers. As a consequence, they started a campaign of deportations to concentration camps throughout Libya, Tunis, Germany, Italy and Austria. Cyrenaican Jews were transferred to the concentration camp of Jado (235 km south of Tripoli), where 2.584 individuals were interned in 1942. In this camp, Italian officers did not spare any kind of abuse [24]. Tripoli and Jado were liberated by Britain on January 1943, but the situation of the Jews continued to be dramatic. Pogroms took place under the British administration between 1945 and 1948. In 1951, after the establishment of the State of Israel, people were forced to leave *en masse* [25]. By 1960s the Libyan Jewish community, which numbered 38.000 in 1948, had almost entirely disappeared [25].

It should not be forgotten, however, that a significant number of psychiatrists were oppressed by Fascism. Just to name two, Gustavo Modena, director of the psychiatric hospital of Ancona (1913-1938) and vice-president of the SIP when the racial laws were issued, was dismissed from his post because he was Jewish, while Luigi Scabia, director of the asylum of Volterra (1900-1934), was persecuted and removed from his position because accused of being an anti-fascist.

FIGURE 1.
Arturo Donaggio.

Psychiatric hospitals during World War II and the deportations of Jewish patients

After Italy entered the war in 1940, the situation of patients worsened dramatically and it became even more severe in 1942-3. The difficulties determined by the war and the scarcity of material and economic resources impacted both on the general population and on the entire healthcare system. Mental hospitals were the mostly affected, as the psychiatric sector had from always been the least safeguarded and the most marginal one [26]. People in psychiatric hospitals suffered from terrible hygienic conditions, lack of food and clothes, absence of heat, water, and electricity, shortage of medicines and doctors, and epidemics of diseases such as tuberculosis and typhoid fever[17]. Moreover, many asylums found themselves close to military targets (such as military bases, airports and

railways) or to the front line. On 8th December 1943, 28 people died in the psychiatric hospital of Ancona when bombs hit the building. In early July 1944, the asylum of Volterra found itself at the centre of combats that left 10 people dead and 40 injured. On 8th January 1944, 1200 bombs hit the asylum of San Lazzaro in Reggio Emilia: they killed 81 people and severely injured other 53. After the Allied invasion of Sicily, instead, the asylum of Siracusa was occupied by troops and patients were transferred to unhygienic and utterly inadequate buildings [26]. These factors caused a surge in the percentage of people dying in mental hospital, from 6% in 1931-1940 to 14% in 1942-45, while the annual mortality of the general population stood at around 15 per 1000 in 1942-3 [18 27]. Mortality rates were greatest in 1942-43, especially in Southern Italy. They reached 20% in the asylum of Imola, 21% in that of Volterra, and up to 50% in the psychiatric hospitals of Siracusa and Palermo [26]. These data indicate a 60-fold higher mortality in psychiatric hospitals compared to the general population. Overall, about 300 persons (patients and staff) were victims of bombardments and other war activities, while 24.000 to 30.000, according to different reports, died due to the deprivations of war [19].
Other dramatic events concerned the deportations of psychiatric patients from Italian asylums towards Germany and concentration camps in Eastern Europe. In accordance with law n. 1241 of 21th Aug 1939, persons of German origin and resident in the district of Alto-Adige, and in small part in the province of Udine, were given the opportunity to acquire German nationality and emigrate to Germany. On 26th May 1940, after having opted for German nationality, 240 patients of the psychiatric hospital of Pergine (Trento) and other 59 people were collected and transferred to the hospital of Zwiefalten. From the analysis of the available medical reports and other official documents, it emerged that the majority of patients were probably not able to make conscious and free choices regarding the option; there is evidence, instead, that Italian authorities intervened substantially to send as much people as possible to Germany, in order to get rid of them [28 29]. Some patients were later dislocated to other asylums. The majority of patients died in mental hospitals due to deprivations and starvation.
In October 1943, Germany created the Operational Zone of the Adriatic Littoral (*Adriatishes Küstenland*), which included the occupied territories in the Northern-Adriatic zone. Consequently, the persecution of the Jews present in this area turned to physical elimination. On 28th March 1944, the SS took 39 Jewish

FIGURE 2.
The first number of the journal "The defence of the race" (*La difesa della razza*), edited by the fascist intellectual Telesio Interlandi. First published in August 1938, the journal aimed at promoting racial ideology and anti-Semitism.

people away from the psychiatric hospital of Trieste and, according to their clinical records, brought them towards an "unknown destination". This resulted to be the concentration camp of Auschwitz, where all patients, except for one, died [30]. The same probably happened to the 5 Jews deported from the psychiatric hospital of San Clemente (6th October 1944) and to the 6 deported from San Servolo (11th October 1944), in Venice, although in this case it was not possible to ascertain the destination with certainty [31].
People from these hospitals included not only psychiatric patients, but also political opponents and individuals who took shelter into the asylums to escape from persecutions.

Bending the historical facts

For decades, Italian historiography did not appropriately discuss the facts related to the support of the SIP to fascist racism and to the conditions of psychiatric hospitals during the war. Instead, the responsibilities of Italian authorities and of the individuals

implicated were mitigated. In general, not only fascist propaganda during the war but later historians promoted the narrative "Italians are good people" (*Italiani brava gente*) [32 33]. Consequently, there was a serious delay in reporting issues concerning Italian racism, anti-Semitism and the racial laws. These were considered mild as compared with those of Nazi Germany [17 32]. The Italian population was portrayed as a victim of the Fascist regime and of the war, the responsibility for which was attributed to "bad Germans" [34]. In truth, although the alliance with Nazi Germany exerted some influence, Italian racism was not something just imported from Germany [35]. Italian authorities actively collaborated to the implementation of the "Final Solution" [17 35] that, as we have seen, involved people in psychiatric hospitals. The subject of the reaction of Italians to the racial laws has long been debated. For a long time it was argued that the majority of Italian people were more or less openly hostile to the anti-Jewish legislation and that anti-Semitism lacked any real consistency or popular tradition [36]. Recent studies offer a more complex portray that challenges this interpretation [37 38]. The notes of the police demonstrate that no one segment of society manifested any public objection to the racial laws [37]. After these were issued, there was a great public interest in the "Jewish question", especially in those sectors of the economy where the presence of the Jews was most significant [37]. This interest diminished only after living conditions began to deteriorate during the course of the war. Closer examinations of Italians reactions to anti-Semitic policies indicate that sympathy may have been expressed on an individual level; however, many social groups contributed actively to excluding Jews from public life [37].

Discussions regarding the psychiatric field started even later and they reached the general public with difficulty and exerted a lesser impact than information on the Holocaust [39]. In an effort to get back to normal, the SIP returned to the scientific issues it was working on before the war. The role the society played in promoting fascist ideology and racism and the adherence of Donaggio to the Manifesto of Racist Scientists were kept silent [18]. Still today, Donaggio is often remembered just for his scientific contributions to neurology. It can be argued that during Fascism and the war, Italian psychiatry proved extremely negligent towards its patients. Although it is difficult to ascertain individual responsibilities of psychiatrists, and despite there were doctors who were persecuted in first person and who refused to collaborate with the regime, the psychiatric sector proved guilty of leaving its patients exposed to war actions and repressions. At the same time psychiatric institutions were insufficient in the provision of care [18 30]. In answering the question of whether there was an intentional effort to kill the mentally ill, Peloso [27] indicates a number of evidence that are against this hypothesis. First of all, Italian psychiatry and the eugenics movement never approved euthanasia of the incurably ill. Notwithstanding, in agreement with Peloso [18 27] and Padovani and Bonfiglioli [40], we argue that the responsibilities are not diminished by the likely lack of intentionality. This applies to those implicated, whether by promoting racism and anti-Semitism, by actively collaborating to oppressions and deportations, or by neglecting patients in need.

Connecting to the present

The legacy of eugenic has not been eradicated. After World War II, forced sterilization remained a routine legal option for patients affected by mental disorders in the US until 1978, in Sweden until 1982 and in Switzerland until 1992. In Italy, more than 6.000 compulsory sterilizations were carried out between 1985 and 1998; furthermore, the CGIL published the case of 107 women who were asked to present a certification of sterilization for an employment [41]. At present, advances in genetic research have raised concerns that genetic information may be used for discriminatory purposes, for example by insurance companies and employers [2]. At the same time, the use of asylums for political reasons did not end with the war. In 1945, hundreds of partisans were arrested and tried for crimes such as ruthless executions of suspected fascists and collaborators [13]. In 1946 the Italian justice minister, Palmiro Togliatti, issued a general amnesty in the name of "national reconciliation". Eight days later, 7.106 fascists, but only 153 partisans, had been able to benefit from it. In 1955 it was estimated that, over the 10-year period after the end of the war, 2.474 partisans had been arrested and, of these, 1.007 condemned [13]. To avoid heavy convictions, many left-wing attorneys advocated the recognition of insanity and the admission of partisans to psychiatric hospitals (many were then transferred to the asylum of Aversa). Due to repeated renewals of detention motivated by "social dangerousness", these individuals spent years into asylums (three to five years on average, but up to more than ten in some cases) without suffering from any mental disorder, deprived of their rights and exposed to abuse [13]. Although aberrations such as those described above

do not depict the essence of psychiatry, they can not be dismissed as accidents nor be considered as buried in the past [42]. Psychiatry has gone through profound processes of change over the last decades. Mentally ill patients, however, continue to represent a vulnerable portion of the population and issues remain around this science. The mainstream model of contemporary psychiatry to explain the aetiology of mental disorders is the biopsychosocial model [43 44]. Mental illnesses have a multi-factorial aetiology, with no factor taken singularly exerting a linear causality. As a consequence, the definition of psychiatric disorders depends largely on the values and cultural norms of a society [45], which in turn may expose psychiatry to political and ideological attentions and to different forms of abuse [42].

All over the world, human rights of people with mental disorders and psychosocial disabilities are violated [46 47]. These individuals experience stigma and discrimination, are vulnerable to violence and abuse, and often lack access to adequate treatment and care. Furthermore, they achieve poorer educational and occupational outcomes and are prevented from participating fully in society [48]. Up to this year, the Italian forensic system was based on six forensic mental hospitals (*Ospedali Psichiatrici Giudiziari* – OPGs). These were located in obsolete facilities with heavy use of custodial staff and the quality of healthcare was seriously unsatisfactory [49]. For this reasons, in 2006 the Council of Europe issued a warning for violation of human rights. Furthermore, it is possible that such facilities were used to protect criminals who did not have any mental disorder. On 17th February 2012 a new law (9/2012) was passed that established the closure of OPGs and the creation of new facilities in order to provide adequate care to socially dangerous individuals. However, criticism has been raised about the suitability of such facilities to achieve this aim [49]. Finally, high levels of psychiatric morbidity are reported in people detained in prisons in many countries, yet many prisoners are not provided proper, if any, treatment [50 51].

To conclude we argue that, far from consigning it to oblivion, we need to acknowledge our past and maintain a full awareness of our history. This represents a fundamental step in the process of gaining a full historical awareness and of taking responsibilities for the crimes that were committed. Furthermore, such move needs to be accomplished not only by psychiatrists as single individuals, but also by the association of Italian psychiatry. In fact, historical awareness is the essential element that makes reconciliation possible: first, it is a mean for reinstating human dignity at the heart of psychiatric practices; second, it allows psychiatrists to reconcile with the history of their profession and strengthen their professional integrity. There are factors suggesting that psychiatry may be still at risk for misuse in the future. However, what happened during the Fascist era and World War II owns a historical value. It may guide us in dealing with current ethical issues, such as prenatal diagnosis, genetic research and testing, and physician-assisted suicide. In this sense, what we learn from the past can guide us in dealing with future challenges.

Take home messages for psychiatric care

- Italian Psychiatry has had an active role during fascism supporting racial lows
- Patients admitted to psychiatric hospitals suffered from severe deprivations, which caused a 60-fold increased mortality
- The SIP has failed to recognize and properly discuss these events
- It is never to late to take a pardon
- Knowledge of the own history and cautious actualization is the an essential part of ethical approaches in a modern Psychiatry

References

1 Galton F. *Eugenics: its definition, scope, and aims.* Am J Sociol 1904;10:1-25.
2 Sfera A. *Can psychiatry be misused again?* Frontiers in Psychiatry 2013;4(Article 101).
3 Binding K, Hoche A. *Die Freigabe der Vernichtung lebensunwerten Lebens: Ihr Maß und ihre Form*. Berlin: Leipzig 1920.
4 Torrey EF, Yolken RH. *Psychiatric genocide: Nazi attepts to eradicate schizophrenia.* Schizophr Bull 2010;36:26-32.
5 Schneider F. *Psychiatrie im Nationalsozialismus – Erinnerung und Verantwortung.* Nervenarzt 2011;82:104-20.
6 Kaelber L. *Jewish children with disabilities and Nazi "euthanasia" crimes.* Bull Carolyn Leonard Miller Center Holoc Stud 2013;17:1-23.
7 Proctor R. *Racial hygiene: medicine under the Nazis*. Cambridge, MA: Harvard University Press 1988.
8 Cassata F. *Una storia da scrivere: l'eugenica in Italia.* Medicina & Storia 2005;9:133-41.
9 Cassata F. *Between Lombroso and Pareto: the Italian way to eugenics*. In: Cassata F, editor. *Building the New Man: eugenis, racial science and genetics in twentieth-century Italy*. Budapest-New York: Central European University Press 2011.
10 Peloso PF. *Morselli's views on eugenics.* History of Psychiatry 2003;14:269-70.
11 Piccinelli M, Politi P, Barale F. *Focus on psychiatry in Italy.* Br J Psychiatry 2002;181:538-44.
12 Piazzi A, Testa L, Del Missier G, et al. *The history of Italian psychiatry during Fascism.* History of Psychiatry 2011;22:1-17.
13 Franzinelli M, Graziano N. *Un'odissea partigiana. Dalla resistenza al manicoimo*. Storie. Milano: Feltrinelli 2015.
14 Petracci M. *I matti del Duce. Manicomi e repressione politica nell'Italia fascista*. Roma: Donzelli Editore 2014.
15 Peloso PF. *The birth of Italian Society of Psychiatry.* Evidence-based Psychiatric Care 2015;1:3-9.
16 Fernando S. *Race and culture issues in mental health and some thoughts on ethnic identity.* Couns Psychol Q 2012;25:113-23.
17 Israel G, Nastasi P. *Scienza e razza nell'Italia fascista*. Bologna: il Mulino 1998.
18 Peloso PF. *La guerra dentro. La psichiatria italiana tra fascismo e resistenza (1922-1945)*. Verona: Ombre corte 2008.
19 Brancaccio MT. *Where have all the traumatized people gone? World War II and its aftermath in Italy: trauma and oblivion*. In: Withuis J, Mooij A, editors. *The politics of war trauma. The aftermath of World War II in eleven European countries*. Aksant Academic Publishers: Amsterdam 2010.
20 Bernardini G. *The origins and development of racial anti-Semitism in fascist Italy.* J Modern Hist 1977;49:431-53.
21 Cavarocchi F. *Il censimento degli Ebrei dell'agosto 1938.* La rassegna mensile di Israel 2007;73:119-30.
22 Zuccotti S. *L'olocausto in Italia*. Milano: Tea storica 1995.
23 Picciotto L. *Il Libro della Memoria. Gli ebrei deportati dall'Italia*. Milano: Ricerca della Fondazione Centro di Documentazione Ebraica Contemporanea. Mursia 2002.
24 Roumani MM. *The Jews of Libya: Coexistence, Persecution, Resettlement*. Eastbourne: Sussex Academic Press 2008.
25 Aharoni A. *The Forced Migration of Jews from Arab Countries.* Peace Review 2003;15:53-60.
26 Sorcinelli P. *La follie della guerra. Storie dal manicomio negli anni quaranta.* Milano: Franco Angeli 1992.
27 Peloso PF. *Psychiatry and psychiatric patients in Italy during World War II.* Int J Ment Health 2006-2007;35:66-80.
28 Arreghini E. *Volenti, nolenti o incapaci di intendere?* In: Perwanger V, Vallazza G, editors. *Follia e pulizia etnica in Alto Adige. Atti del convegno. Bolzano 10 marzo 1995*. Centro di Documentazione di Pistoia: Pistoia 1995.
29 Steurer L. *Un capitolo dimenticato della storia sudtirolese. Trasferimento e anniettamento dei malati di mente Sudtirolesi nel quadro del programma di eutanasia del nazionalsocialismo*. Sturzflüge, Bolzano: Südtiroler Kulturzentrum & Südtiroler Autorenvereinigung 1982.
30 Norcio B. *L'Adriatisches Kunsteland e la deportazione psichiatrica del 1944 dall'Ospedale Psichiatrico di Trieste*. In: Fontanari D, Toresini L, editors. *Psichiatria e nazismo. Atti del convegno. San Servolo 9 ottobre 1998*. Centro di Documentazione di Pistoia: Pistoia 1998.
31 Lallo A, Toresini L. *La deportazione ebraica dagli ospedali psichiatrici di Venezia nell'ottobre 1944. Storia e contenuti*. In: Fontanari D, Toresini L, editors. *Psichiatria e nazismo. Atti del convegno. San Servolo 9 ottobre 1998*. Centro di documentazione di Pistoia: Pistoia 1998.
32 Rodogno D. *Italiani brava gente? Fascist Italy's policy towards the Jews in the Balkans, April 1941 - July 1943*. European History Quarterly 2005;35:213-40.
33 Del Boca A. *Italiani, brava gente?* Vicenza: Neri Pozza 2005.
34 Focardi F. *Il cattivo tedesco e il bravo italiano. La rimozione delle colpe della seconda guerra mondiale*. Storia e Società. Roma-Bari: Laterza 2013.
35 Wildvang F. *The enemy next door: italian collaboration in deporting Jews during the German occupation of Rome.* Modern Italy 2007;12:189-204.
36 De Felice R. *Mussolini il duce. Lo stato totalitario (1936-1940)*. Torino: Einaudi 1981.
37 Galimi V. *The "new racist man". Italian society and the fascist anti-Jewish laws*. In: Albanese G, Pergher R, editors. *In the society of Fascists: acclamation, acquiescence, and agency in Mussolini's Italy*. Palgrave Macmillan: New York 2012.
38 Visani A. *Italian reactions to the racial laws of 1938 as seen through the classified files of the Ministry of Popular Culture.* J Modern It Stud 2006;11:171-87.
39 Von Cranach M. *La psichiatria nel periodo nazista*. In: Norcio B, Toresini L, editors. *Psichiatria e Nazismo*. Centro di Documentazione di Pistoia: Pistoia 1994; pp. 29-37.
40 Padovanim G, Bonfiglioli L. *Le vicende storiche e statistiche dell'assistenza psichiatrica in Italia durante la seconda guerra mondiale.* Rivista Sperimentale di Freniatria 1948;52:375-96.
41 Comitato Nazionale per la Bioetica. *Il problema bioetico della sterilizzazione non volontaria*. Presidenza del Consiglio dei Ministri. Dipartimento per l'Informazione e l'Editoria - 20-11-1998.
42 Jablensky A. *The nature of psychiatric classification: issues beyond ICD-10 and DSM-IV.* Aus NZ J Psychiatry 1999;33:137-44.
43 Engel GL. *The clinical application of the bio-psycho-social model.* Am J Psychiatry 1980;137:535-44.
44 Ghaemi N. *The rise and fall of the biopsychosocial model.* Br J Psychiatry 2009;195:3-4.
45 Anderson B, Khoo R. *Mental illness: diagnosis or value judjment?* Br J Nurs 1994;3:957-9.
46 Drew N, Funk M, Tang S, et al. *Human rights violations of people with mental and psychosocial disabilities: an unresolved global crisis.* Lancet 2011;378:1664-75.
47 Jarab J. *Psychiatry and human rights: a difficult relationship, but with a growing potential.* Neuropsychiatry 2015;29:106-11.
48 Funk M, Drew N, Freeman M, et al. *WHO. Mental health and development: targeting people with mental health conditions as a vulnerable group*. World Health Organization 2010.
49 Barbui C, Saraceno B. *Closing forensic psychiatric hospitals in Italy: a new revolution begins?* Br J Psychiatry 2015;206:445-6.
50 Fazel S, Danesh J. *Serious mental disorder in 23.000 prisoners: a systematic review of 62 surveys.* Lancet 2002;359:545-50.
51 Fazel S, Seewald K. *Severe mental illness in 33 588 prisoners worldwide: systematic review and metaregression analysis.* Br J Psychiatry 2012;200:364-73.