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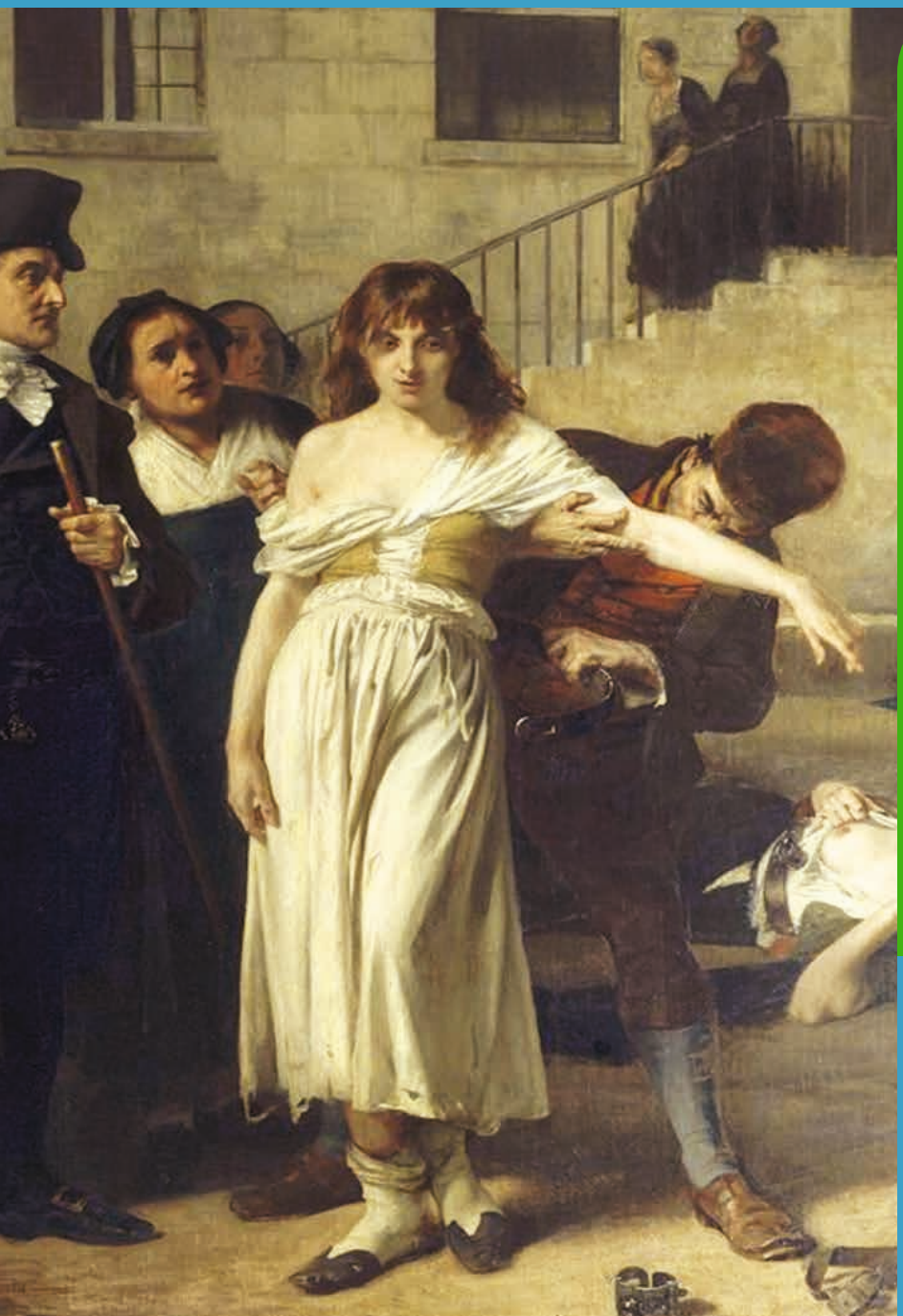

Evaluation of an educational intervention for reducing mental health stigma in media professionals
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Pharmacological properties and innovative therapeutic targets of novel compounds used to treat major depression
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Books:

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

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EVALUATION OF AN EDUCATIONAL INTERVENTION FOR REDUCING MENTAL HEALTH STIGMA IN MEDIA PROFESSIONALS

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Summary

Objectives: Media professionals represent an important target group for anti-stigma interventions. This pilot study aims to assess the effect of an educational intervention delivered to a group of media professionals and it was designed to improve their knowledge on mental health issues and attitudes towards persons with mental health problems.

Materials and methods: This study was conducted following a pre-test post-test design. A total of 60 newspaper journalists attended a one-day training course on mental disorders, mental health legislation and most common prejudice towards people with mental health problems and completed a pre- and post- modified version of the Community Attitudes toward the Mentally Ill (CAMI) questionnaire.

Results: Prior to intervention, 30% of the sample had a poor knowledge on mental health issues. After the intervention, participants displayed an increased level of knowledge on the most appropriate terminology to identify main mental disorders; an increased percentage of participants declared that they were not able to recognize persons with mental disorders on the basis of their behaviour (from 15 to 31.7%) and a reduced percentage of participant endorsed a dangerousness stereotype (from 16.7 to 5%). Also, it has been registered a decreased number of people judging as inappropriate the closing of psychiatric hospitals (from 46.7 to 20%) and of those asking for the restoration of psychiatric hospitals (from 40 to 18,3%).

Conclusions: This study shows that one anti-stigma education session can be effective in improving knowledge on mental health and attitudes towards persons with mental health problems in media professionals in the short term.

Key words: stigma, prejudice, mental health, mass media, journalists

Introduction

Quality of life and social integration of persons with mental health problems do not simply relay on the care they receive, but also on the attitude shown by people they meet in their everyday life, on the opportunities to make use of the services available in the community and on the expectations of the community where they live [1]. On the other hand, mental health stigma has a negative impact on people with mental health problems, as they stir up feelings of helplessness and shame with the consequent risk of refusing treatment or delaying access to services [2-4]. This triggers a vicious circle of self-exclusion, isolation and marginalization [5-8]. Programmes aimed to reduce mental health stigma have not always been able to achieve their goals [9-11]. This is most likely due to an inaccurate selection of target groups [12]. Some authors, in fact,

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suggest that anti-stigma programmes addressing the general population are not effective, whereas it is seems more useful if they focus on specific target groups, such as high school students, medical students, healthcare professionals, police officers and media professionals [13-16].

This latter group represents a very important target for anti-stigma programmes, as mass media play a major role in perpetuating a negative picture of people with mental health problems [17-19]. Media commonly report mental health issues as associated with violent behaviours and crimes [20]. On the other hand, media may be a key resource for implementing and disseminating effective anti-stigma initiatives [21 22]. Their appropriate use of mass media messages may represent an added value in anti-stigma campaigns, as they offer the possibility to convey clear and demystifying messages, reaching a large number of potential recipients.

Considering the major role played by mass media in shaping the public opinion, we implemented an educational anti-stigma intervention for media professionals, which was specifically designed to improve their knowledge on mental health issues and their attitudes towards persons with mental health problems. The present study aims to report on the effectiveness of this educational intervention over the short term.

Methods

Study design

This research used a quasi-experimental pre-test post-test design, in which a group of media professionals was evaluated with a standardized measure before and after an educational intervention.

The evaluation questionnaire

Data collection was performed by using an *ad hoc* assessment measure adopted in previous investigations on the opinions about mental disorders and psychiatric care in the general population and healthcare professionals in Italy [23]. It is a self-rated questionnaire composed of 46 items divided into five sections: 1) Information on personal characteristics of respondents, 2) information on mental disorders, 3) attitude towards people with mental disorders, 4) information on psychiatric care/legislation, 5) opinions on psychiatric care. The items of sections 2 and 3 were taken from the Community Attitudes toward the Mentally Ill (CAMI) inventory [24 25], whereas the items of sections 4 and 5 were taken from an Italian questionnaire previously used in a research on the information and opinion of the general population on psychiatric care [26]. The questionnaire was administered 30 minutes before the start of the educational intervention and re-administered after its attendance. Confidentiality and anonymity was guaranteed to all participants.

Participants

The intervention was provided within the framework of an accredited professional training course (ECM) organized by the University of Verona. No specific characteristics were required to attend the course, neither about the specific medium (press, television, web, radio), nor about the working area (politics, economics, health, sports, educational, crime, gossip). Seventy-one newspaper journalists participated; sixty of them filled out and gave back the questionnaires both before and after the intervention.

The intervention

The intervention was designed as an educational module aimed at helping journalists to gain a better knowledge and understanding of mental health issues. The intervention lasted four hours and was structured as a teacher-led lesson followed by a group discussion. The intervention addressed the following issues: 1) definition and description of most common mental disorders, 2) challenging the most common prejudices about mental disorders (ie, dangerousness, unpredictability, incurability, incomprehensibility), 3) information on mental health services organization and core elements of Italian mental health legislation, 4) role of mass media in increasing or reducing mental health stigma, with specific emphasis to a more accurate/appropriate use of terminology when reporting on mental health issues. With this latter regard, the course underlined how an inappropriate/inaccurate use of language by mass media might contribute to reinforce the negative image of people with mental health problems; on the other hand, it was also pointed out how media might represent a very strong de-stigmatizing tool. Recommendations provided by the main media reporting guidelines available at international level (eg, 'Time-to-Change' in the UK, 'Mindframe' in Australia and 'Mindset' in Canada), together with recommendations of a proposed code of ethics for Italian journalists on mental health reporting ('Carta di Trieste'), were taken into account and discussed. At the end of the course it was given to participants a list of words that should be used or avoided when reporting on mental health issues.

Statistical analysis

Considering the qualitative nature of the variables in analysis, analysis was carried by using descriptive statistics (distribution of frequency) and non-parametric analysis (Chi-square test). All analysis are elaborated through the statistical software *Statistical Package for Social Sciences (SPSS) for Windows,* version 10.1.

Results

Socio-demographic characteristics of participants who returned the completed questionnaires are shown in Table I.

Knowledge on mental disorders

As shown in Table II, the vast majority of participants (88%) knew the name of at least one psychiatric disorder: most of them (53%) mentioned "schizophrenia", followed by "bipolar disorder" (31%) and "depression" (26.7%). It is important to underline that among participants who declared to know the name of at least one mental disorder, 15% did not show an adequate level of knowledge, since they reported not pertinent or inexistent psychiatric conditions (eg, '*raptus*', 'madness', 'hysteria', 'senile dementia', 'autism').
The level of uncertainty among participants was even higher when considering the definition of "mental retardation": 68% declared to know what it was, but nearly 52% was not able to mention any condition that implied a mental retardation (while only 13% mentioned a correct diagnosis, such as Down's syndrome). Intuitively, the majority of participants (78.3%) seemed to be aware that there was a difference between this kind of conditions and a mental disorder. Forty-five per cent declared to be able to recognize people with mental health problems on the basis of their behaviour (53.3%) and their way of speaking (41.7%), whereas physical appearance seemed a less influential element (10%) (see Table III).
Regarding the causes of mental disorders, a great level of uncertainty was found, since only 31.7% of participants declared that the causes of mental diseases are well known. Similarly, the potential for a genetic transmission to offspring was somewhat uncertain (31.6% had no opinion on this, whereas 16.7% reported that mental disorders can be genetically transmitted to offspring).
Here is an interesting finding regards the *association between violence* and *mental disorders:* just a minority of participants (16.7%) reported that people with mental health problems are more aggressive than other people. A low degree of prejudice was also found with regard to intellectual level, since the vast majority of participants (85%) reported that the IQ of people with mental health problems was not necessarily lower than the general population.

Table I. Socio-demographic characteristics of participants (n = 60).

		N	%
Gender	Male	31	51,7
	Female	29	48.3
Marital Status	Single	23	38.3
	Divorced	9	15.0
	Married/Living with partner	27	45.5
Education	Junior high school	2	3.4
	Secondary school	17	28.3
	University degree	41	68.3
Job	Free lance professional	21	35.0
	Employee	18	30.0
	Retired	4	6.7
	Currently unemployed	1	1.7
	Other	16	26.6

Table II. Knowledge of mental disorders ("*Can you write down some names of mental disorders*?"): comparison between pre- and post- intervention.

	Baseline	Follow-up
Schizophrenia	53.3%	83.3%
Bipolar Disorder	31.7%	40.0%
Depression	26.7%	50.0%
Inappropriate response	15.2%	6.8%
No response	15.0%	8.0%

Attitude towards people with mental health problems

As shown in Table IV, 55% of participants reported that if a psychiatric patient had moved near to their home, he/she would have been treated "differently" by the other people in the neighbourhood. However, only for 23%, of them the presence of people with mental health problems in their own neighbourhood would lead to open manifestations of opposition.
It is interesting to note that the tendency to discriminate psychiatric patients is usually attributed to other people rather than self acknowledged: in fact, only 10% of participants openly admitted that they would display a 'different' (discriminatory) behaviour toward a person with mental health problems who might have moved to their neighbourhood.

Table III. Knowledge on mental disorders: comparison between pre- and post- intervention (Chi-square).

	baseline			follow-up			p
	Yes	No	Do not know	Yes	No	Do not know	
Do you know the name of a mental disorder?	88.3%	8.3%	3.3%	95.0%	3.3%	1.7%	n.s.
Do you know what 'mental retardation' means?	68.3%	11.7%	20.0%	70.0%	8.3%	21.6%	*
Is there any difference between 'mental disorder' and 'mental retardation'?	78.3%	3.3%	18.4%	76.7%	6.7%	16.6%	n.s.
Are you able to recognize a person with a mental disorder?	45.0%	8.3%	46.7%	36.7%	26.7%	36.7%	*
Are people with mental disorders recognizable by what they say?	41.7%	28.3%	30.0%	45.0%	36.7%	18.3%	*
Are people with mental disorders recognizable by what they do?	53.3%	15.0%	31.7%	50.0%	31.7%	18.3%	*
Are people with mental disorders recognizable by their appearance?	10.0%	66.7%	23.4%	6.7%	78.3%	15.0%	*
Are the exact causes of mental disorders known?	31.7%	41.7%	26.7%	33.3%	46.7%	20.0%	*
Can mental disorders be transmitted to offspring?	16.7%	51.7%	31.6%	15.0%	63.3%	21.7%	*
Do you know someone who has suffered from a mental disorder?	71.7%	25.0%	3.3%	76.7%	21.7%	1.7%	*
Have you ever suffered from mental disorder?	11.7%	86.7%	1.7%	13.3%	86.7%	0.0%	*
Has someone in your family ever suffered from a mental disorder?	26.7%	63.3%	10.0%	30.0%	61.7%	8.3%	*
Compared to others, people with mental disorders are…	More dangerous	No difference	Less dangerous	Not know	More dangerous	No difference	Less dangerous	Not know	p
	16.7%	70.0%	0.0%	13.3%	5.0%	90.0%	0.0%	5.0%	*
Compared to others, people with mental disorders are…	More intelligent	No difference	Less intelligent	Not know	More intelligent	No difference	Less intelligent	Not know	
	5.0%	85.0%	3.3%	6.7%	3.3%	91.7%	1.7%	3.3%	*

** p < 0.001*

When exploring availability to work with a person with mental health problems, 45% of the sample declared to be willing to do it. However, 58% declared that they did not have that chance to attend places and situations also attended by persons with mental health problems It is interesting to note that 15% of respondents believed that it was right that a person could feel guilty for his/her mental health problem.

If asked about a possible charity project to which they would donate, 56% declared that they would donate money to sick children, nearly one third to cancer patients, whereas nobody declared that they would donate to people with mental disorders.

Information and opinions about psychiatric care

The vast majority of participants (97.7%) were aware that psychiatric hospitals in Italy had been closed; however, not all of them knew that this closure was

Table IV. Attitudes towards people with mental disorders: comparison between pre- and post- intervention (Chi-square).

	Baseline			Follow-up			p
	Yes	No	Do not know	Yes	No	Do not know	
If a person with mental disorder would be your neighbour, do you think that people would treat him differently from others?	55.0%	15.0%	30.0%	61.7%	13.3%	25.0%	*
If a person with mental disorders would be your neighbour, do you think that he would find opposition from the neighbourhood?	23.3%	30.0%	46.7%	43.3%	13.3%	43.0%	*
Would you personally treat him differently from others?	10.0%	51.7%	38.3%	6.7%	58.3%	35.0%	*
If a person with mental disorders would be your neighbour, could it be a problem for you?	6.7%	61.7%	31.7%	8.3%	65.0%	26.7%	*
Would you work together with a person suffering from mental disorder?	45.0%	11.7%	43.3%	55.0%	8.3%	36.7%	*
Are you usual to frequent some places (Do you usually spend time in places) frequented by people with mental disorder?	23.3%	58.3%	18.3%	28.3%	56.7%	15.0%	*
Do you believe that's fair that people may feel guilty because of their mental disorder?	15.0%	80.0%	5.0%	8.3%	86.7%	5.0%	#
Would you feel comfortable to talk with friends about a relative with mental disorder?	71.7%	16.7%	11.7%	60.0%	25.0%	15.0%	*
For which disorder would you prefer to make charitable donations?	Diabetic	Mental	Pediatric	Cancer	Diabetic	Mental	Pediatric	Cancer	
	0.0%	0.0%	56.6%	35.0%	0.0%	10.0%	51.7%	33.3%	*

** p < 0.001; # p < 0.05*

the consequence of the Italian Psychiatric Reform Law (the "Law n. 180") (see Table V).

Regarding the attitude toward mental health care (see Table VI), less than half of participants (46.7%) considered as inappropriate the closure of psychiatric hospitals and 40% asked for the restoration of hospitalization within psychiatric hospitals.

Half of participants did not express a clear opinion on whether the principles contained in the Italian Psychiatric Reform Law has had practical application,

Table V. Information on Italian mental health care: comparison between pre- and post- intervention (Chi-square).

	Baseline			Follow-up			p
	Yes	No	Do not know	Yes	No	Do not know	
A law approved in Italy in 1978 establishes that nobody who is suffering from mental disorder can be hospitalized in a psychiatric hospital. In case of crisis, the treatment can be provided in a psychiatric ward in a general hospital. Out of the crisis psychiatric care is provided in facilities outside the hospital. Did you know about that?	80.0%	18.3%	1.7%	96.7%	1.7%	1.7%	n.s.
Did you know at least that in our Country psychiatric hospitals have been permanently closed?	96.7%	0.0%	3.3%	98.3%	0.0%	1.7%	n.s.

whereas those endorsing a positive answer to this question are only 16.7%. A negative attitude towards the current psychiatric legislation is also evident by the item exploring the burden posed on families by community care as prescribed by Law n. 180, since 66.7% of respondents found family burden as "excessive". However, there is a large consent (61.7%) on the possibility of placing patients discharged from

Table VI. Opinion on Italian mental health care reform: comparison between pre- and post- intervention (Chi-square).

	Baseline			Follow-up			p
	Yes	No	Do not know	Yes	No	Do not know	
Do you consider appropriate the closure of psychiatric hospitals?	38.3%	46.7%	15.0%	65.0%	20.0%	15.0%	*
Was it a good idea to discharge patients from psychiatric hospitals in order to treat them outside?	61.7%	15.0%	23.4%	75.0%	10.0%	15.0%	*
Do you believe that psychiatric reform law has been put into operation?	16.7%	33.3%	50.0%	40.0%	13.3%	46.7%	#
Do you believe that the psychiatric hospitalization should be restored?	40.0%	35.0%	25.0%	18.3%	61.7%	20.0%	*
Do you believe that the current situation of psychiatric care represents an excessive burden on patients' families?	66.7%	1.7%	31.7%	61.7%	6.7%	31.7%	*
Compared to the traditional hospital care, community care, is…	More expensive	Less expensive	Do not know	More expensive	Less expensive	Do not know	
	20.0%	25.0%	55.0%	23.3%	28.3%	48.3%	*
The psychiatric reform law should be…	Maintained	Modified/ Abolished	Do not know	Maintained	Modified/ Abolished	Do not know	
	15.0%	46.7%	38.3%	36.7%	46.7%	16.7%	*
The consequences of mental health care provided according the Law 180 are…	Advantage	Disadvantage	Do not know	Advantage	Disadvantage	Do not know	
	28.3%	20.0%	51.7%	68.3%	10.0%	21.6%	*
The psychiatric care outside the psychiatric hospitals has been…	Positive	Negative	Do not know	Positive	Negative	Do not know	
	28.3%	28.3%	42.4%	63.3%	15.0%	21.7%	*

** p < 0.001; # p < 0.05*

former psychiatric hospitals into small residential facilities located within the community.
The majority of participants (55%) could not express an opinion on the burden posed on families by community care compared to psychiatric care provided within mental hospitals. The judgment on the advantages offered by the current system of psychiatric care seems to be uncertain, since only 15% of participants were favourable to the maintenance of the current mental health legislation, whereas 46.7% would propose a revision. A strong uncertainty on the advantages of community care was found, as nearly half of the sample could not express a clear opinion on it and the remaining part of the sample was equally shared in those endorsing the positive consequences and those the negative ones.

Evaluation of the follow-up after the class

After the intervention, significant differences were found in a number of items of the different sections of the questionnaire.
As shown in Table II, the level of knowledge on mental health terminology significantly increased after the intervention.
Moreover, the percentage of participants reporting not to be able to recognise persons with mental health problems on the basis of their behaviour increased from 15 to 31.7%, the percentage of participants considering people with mental health problems more dangerous dropped from 16.7 to 5%, and the percent of participants declaring that persons with mental health problems have the same level of intelligence raised from 85 to 91.7%. After the intervention, the percentage of participants that would refer to a psychiatrist if a their own family member had experienced some form of mental distress increased from 45 to 50%, similarly to the percentage of participants that indicate psychotropic medication as a possible kind of treatment for psychiatric disorders (from 53.3 to 63.3%) (see Table III).
After the intervention, participants had a greater awareness of the discriminatory behaviours endorsed by other people, showing at the same time a positive change in their own potentially discriminatory behaviour (the percentage of interviewed declaring that would not threaten in a different way a person affected by mental disorder increased from 51.7 to 58.3%). Also the availability of the interviewed to work with people affected by mental disorders increased (from 45 to 55%) (see Table IV). It has been observed a higher empathy and sensibility towards mental disorders, with an important reduction of the percentage of participants believing to be right that a person affected by mental disorder could feel guilty for his disturb, and an increased propensity to make a charitable donation in the field of mental health.
As for the opinions towards psychiatric care (see Table VI), the percentage of participants who considered inappropriate closing psychiatric hospitals in Italy dropped from 46.7 to 20%, along with the proportion of those in favour of their reopening (from 40 to 18.3%). After the intervention, the participants who were in favour of maintaining the current psychiatric legislation increased from 15 to 36%. Moreover, having a community mental health care organization was considered an advantage for an increased number of people (from 28.3 to 68.3%), and the same positive trend is also recorded (from 28.3 to 68.3%) if we enquiry about the positive effects of this organization on patients.

Discussion

Consistent with literature [27-29], the intervention presented in this pilot study has shown a promising effect in reducing mental health stigma in media professionals, at least in the short term run.
The intervention showed a generalized effect in most of the domains addressed in the training course. The main effect was found in improving the knowledge of correct terminology used to define common psychiatric conditions. Prior to the intervention, journalists participating in this study had a poor knowledge of mental health issues, as indicated by high percentages of inappropriate terminology (e.g. "*raptus*", "madness"). After the intervention, knowledge of mental health issues improved significantly. This effect, named as 'mental health literacy' [30], is deemed to be important for dealing with mental health stigma, since a better understanding of mental health issues may lead to a more realistic image of psychiatric conditions and to a reduced social distance towards people with mental health problems. The improved knowledge of mental disorders, combined with a greater trust expressed by participants towards psychiatric treatments (including pharmacotherapy), seems a remarkable achievement if we consider that mass media, as main source of information, do not only mirror attitudes and values, but also contribute to shaping them.
A significant effect was also found on the items exploring the link between psychiatric disorders and aggressiveness/violence. It should be said that prior the intervention a low percentage of participants hold the

prejudice that persons with mental health problems are more dangerous than others. This is a rather interesting finding, since literature reports that mental disorders are often depicted by the mass media as strongly associated with aggression and violence [31]. Possible explanations for this behaviour need further analysis.

The intervention had also a significant impact on improving both the overall attitude towards people with mental health problems and the availability to share common living spaces with persons with mental problems (e.g. living in the same condominium or on the same floor of the building).

To what extent this positive change in attitudes might be translated into actual behaviour in everyday life, is a question difficult to answer. Also other studies evaluating mass media reporting style on mental health issues had conflicting results [32].

Another positive effect of the intervention presented here is a less critical attitude toward the model of mental health care implemented in Italy following the Law n.180. Prior to the intervention, most participants had a critical view of Italian mental health care (e.g. many believed that asylums were still useful or declared to be in favour of a more restrictive change in the current model of community mental health care, due to the excessive burden posed to families). It is likely that this fact may be attributed to a partial and incorrect knowledge of how mental health services function in our country. The possibility of expanding the scope of participants' knowledge *vis-à-vis* the organization and operation of mental health services has contributed to create a clearer and more realistic image of what the critical points are, but also to show the strengths and advantages of the Italian mental health care system. It should finally be pointed out that the participation in the initiative of users and/or of their family members, with their contributions to the living testimony and direct experiences of mental disturbance, would surely have contributed to increasing the effectiveness of the intervention; the presence and the direct contribution of users in support of the anti-stigma initiatives and training to the addressed target group is considered one of the key elements in making them successful or not [33 34]. This message was, however, shared with participants, who were also provided with information on what works or does not in anti-stigma campaigns. Initiatives that are not supported by a correct methodological approach, result in isolated and extemporaneous initiatives, with no verifiable results, which divert resources away from projects that might potentially be more effective. In this regard, it should be noted that the anti-stigma campaigns in Italy are quite heterogeneous as far as their design and purposes are concerned and often burdened by methodological limitations [35].

It should be also acknowledged that this pilot study has a number of limitations. First, the low sample size and the lack of a control group make it difficult to draw definitive conclusions about the effectiveness of the intervention. Moreover, the follow-up evaluation was performed just at the end of the intervention. Previous studies have shown that the effect of anti-stigma programs are likely to lessen with time [36 37]. Therefore, a long-term follow-up evaluation is needed to establish whether the results are maintained over time. Finally, the tendency to answer in a socially desirable way could have influenced the answers given in the after-class evaluation (expectation of changing-improving of the opinions and the concerned behaviours).

Conclusions

The intervention presented in this study has shown some promising effect in reducing mental health stigma in media professional over the short term. However, in order to further confirm this initial finding, studies carried out on larger samples, by using more homogeneous outcomes, and conducted by adopting long-term follow-up time frame, are urgently needed.

Take home messages for psychiatric care

- Media professionals represent an important target group for anti-stigma interventions
- One anti-stigma education session can be effective in reducing mental health stigma over the short term

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PHARMACOLOGICAL PROPERTIES AND INNOVATIVE THERAPEUTIC TARGETS OF NOVEL COMPOUNDS USED TO TREAT MAJOR DEPRESSION

Introduction: unmet needs in the treatment of major depressive disorder

Major depressive disorder (MDD) is one of the most common and disabling psychiatric conditions worldwide and is associated with significant disability and functional impairment [1-3]. Although many medications are available for this complex disorder [4], antidepressant treatment is mainly limited by: delay in the onset of therapeutic effects, poor adherence and adverse long-term effects (in particular weight gain and sexual dysfunction). In addition, according to the STAR*D trial of Nierenberg et al. [5], although most of the investigated patients responded to commonly available psychoactive treatments and achieved remission, they still suffered from at least one residual depressive symptom, which is a known predictor of relapse/recurrence in the long-term. Moreover, non-response to traditional antidepressants is another relevant issue, as more than 20% of MDD patients do not respond or don't recover completely from their illness. These individuals may be considered as affected by treatment-resistant depression [6].

Given that first-line antidepressant medications mainly target the reuptake or breakdown of monoamines, this further highlighted the need to extend the knowledge on MDD pathogenesis and to promote the translation of such findings into novel, effective therapeutic agents. Over the last two decades, research have discovered several novel molecular targets which may be actively involved in the pathophysiology of MDD [4 7 8]. This knowledge has provided intruiging insights into the development of novel antidepressant molecules, some of which have already passed rigorous clinical testing.

The aim of the present review was to summarize the relevant research on novel molecular/cellular targets and recently marketed antidepressant medications which may change the landscape of the treatment of major depression in the near future.

Overview of current treatment strategies with available antidepressant medications

The pharmacological treatment of depression had its inception more than fifty years ago, when tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) were introduced in the clinical world. Later, the 1980s saw the marketing of SSRIs, which presented with a great

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advantage in terms of safety and tolerability [9]; in the early 1990s serotonin and norepinephrine reuptake inhibitors (SNRIs) were introduced, including venlafaxine, desvenlafaxine and duloxetine [10], together with modern SSRIs such as sertraline, paroxetine, and citalopram. The latter are generally regarded as first-line treatment for a depressive episode, but, as stated above, they result in the remission of only a subset of patients.

Whereas, the following treatment options are currently reccomended for patients that do not respond to antidepressant treatment: 1) revision of the psychiatric diagnosis; 2) medication augmentation; 3) switch to another antidepressant medication [11]. The substitution of first-line antidepressant with another first-line medication is currently the most commonly used therapeutic strategy. However, two consecutive trials with different psychoactive medications usually require approximately 6 weeks, and the delay in achieving adequate antidepressant effects is associated with relevant drop-out rates from treatment (al least 50% of patients), which commonly occurs within the first months of treatment [12]. Thus, in order to correctly treat depression and achieve remission it would be fundamental to rapidly identify the correct treatment otption.

Current guidelines advise against combination treatment has been commonly mainly due to the enhanced risk of medication interactions and poor tolerability. Whereas, the use of antidepressant combinations with additive mechanisms of action may represent a useful strategy before augmenting with medications of different classes [13 14]. Interestingly, combining different pharmacological actions affecting multiple monoamine targets is associated with greater efficacy [14]: this reinforces the notion that is may be possible to further improve the outcomes of depression by integrating novel pharmacological agents with different mechanisms of action.

Novel molecular targets of antidepressant drugs: neurotrophins and intracellular pathways

The neurotrophic hypothesis of depression. Neurotrophic factors play a fundamental role in neuronal development, growth, survival as well as neuroplasticity [15-19]. Whereas, chronic stress is associated with a significant reduction in hippocampal neurotrophins levels and volume, as is commonly observed in depression [20]. These and other findings support the neurotrophic hypothesis of depression, postulating that the long-term effects of stress/depression are mediated by a deficiency of neurotrophins [21]. According to this hypothesis, altered neurotrophic signaling is viewed as one of the most relevant factors in the pathophysiology of major depression. Consistently, the latency of antidepressant action is explained with that of neuroplasticity, which is usually occurs after 3-4 weeks of treatment with traditional antidepressant drugs [15 22 23].

Hippocampal neurogenesis is regulated by several neurotrophic factors such as brain-derived-neurotrophic factors (BDNF), insulin-like growth factor I (IGF-I), and vascular endothelium growth factor (VEGF-B) [24-27]. Chronic mild stress has been reported to be associated in animal models with a general reduction of neurogenesis together with reduced hippocampal BDNF levels. Importantly, antidepressant drugs may reverse stress-induced changes and enhance neurogenesis by normalizing BDNF levels [28-30]. Indeed, by inhibiting 5-HT2A/2C receptor, these molecules are able to reverse stress-induced downregulation of BDNF mRNA in the hippocampus leading to adaptations of synaptic strength that may mediate either some short- and long-term behavioral effects of these compounds [31].

Hippocampal neurogenesis may be also enhanced by VEGF [32] as observed by the decline of immature neurons in VEGF-B knockout mice [33]. Kiuchi et al. [34] suggested that VEGF Flk-1 (a Receptor for VEGF) signaling plays a crucial role in ameliorating the adult hippocampal cell proliferation together with the survival of newly hippocampal neurons promoted by antidepressants. Interestingly, after silencing of hippocampal VEGF [35] or using antagonists for its receptor Flk-1 [34], VEGF antidepressant-like properties are interrupted and it has been reported that markers of newborn neurons as doublecortin were drastically reduced. Both electroconvulsive therapy (ECT) [36] and some antidepressant medications are associated with the up-regulation of VEGF, and even the local VEGF administration increases hippocampal neurogenesis. Peripheral administration of IGF, a liver-secreted peptide under the control of growth hormone (GH), was reported to increase hippocampal cell proliferation, enhance exercise-induced increases in neurogenesis [37], and exert antidepressant behavioral effects as well [27 38]. Hoshaw and colleagues [39] reported that central administration of IGF-I is associated with prolonged antidepressant-like activity in the modified rat forced swim test (FST) model. The authors postulated that the behavioral effects of IGF-I were similar to those of BDNF, suggesting that neurotrophins may

be an effective target for the development of novel antidepressant agents. Furthermore, Malberg et al. [40] reported that medications inhibiting binding proteins for IGF-1 (thus, increasing the effects of free IGF-1), may produce both antidepressant-like or anxiolytic effects in mice. Overall, targeting VEGF [34] and IGF [41 42] has yielded interesting results and a new therapeutic strategy to develop innovative antidepressant agents. Other neurotrophic factors such as fibroblast growth factor-2 and nerve growth factor have also been proposed to enhance adult neurogenesis and may serve as novel potential therapeutic targets for the treatment of MDD. However, further studies are required to establish the clinical efficacy and tolerability of neurotrophic agents, and whether their effects are uniquely due to their impact on neuroplasticity [43].

The Cyclic Adenosine Monophosphate Pathway (CAMP) is an important intracellular cascade which is involved in the pathophysiology of major affective disorders; therefore, its components have been generally identified as possible targets for antidepressant agents [44]. Notably, antidepressant-like effects have been provoked in animals by suppressing cAMP degradation with rolipram, or directly injecting cAMP [45 46]. The PKA is activated by cAMP: consequently its activity is increased after chronic treatment with antidepressants [47]. Once PKA is activated, it phosphorylates CREB, the involvement of which in the pathophysiology of major depression is well known. A close interaction between the cAMP cascade and VEGF expression has been suggested by Lee and colleagues [35]; relevantly, antidepressant treatment has been associated with increased VEGF levels [35]. Both BDNF and VEGF genes have been reported to be regulated by CREB [48-51]; CREB, in particular, is a crucial regulator of BDNF synthesis and is virtually involved in most aspects of neuroplasticity [52 53].

Antidepressant medications may not only enhance the phosphorylation of CREB but also the Ca2 +/ calmodulin-dependent protein kinase II [54 55]. Interestingly, chronic treatment with agomelatine has been reported to normalize hippocampal levels of phosphorylated p-CREB, mGlu2/3, and mGlu5 metabotropic glutamate receptors that are involved in the pathophysiology of major depression [56]. It is important to note that some antidepressant drugs such as tianeptine are able to restore stress-induced changes of the transcription factor c-fos, which is considered one of the fundamental markers of the biochemical activity [57 58].

Notably, a novel target for antidepressants activity has been identified in the exchange protein directly activated by cAMP (EPAC) as supported from experimental data emerged from postmortem samples in the hippocampus of depressed individuals [59]. EPAC is able to regulate the release of glutamate in central neurons, but the specific effects of this regulation is still unclear. There are two isoforms of EPAC proteins (EPAC1 and EPAC2), each having multiple domains, with one or two cAMP regulatory binding motifs, respectively [60 61]. EPAC1 and/or EPAC2 proteins are expressed throughout the brain development, particularly in the hippocampus, striatum, and prefrontal cortex formation [45 62]. Dwivedi and colleagues [59] reported that Rap-1, one of the major substrates of PKA, was significantly reduced in the prefrontal cortex and hippocampus of depressed subjects who died by suicide whereas protein level of only Epac-2 was significantly increased in the prefrontal cortex and hippocampus of these individuals.

This differential regulation of Rap-1 and EPAC and their possible involvement in the pathophysiology of depression suggest that these molecules may be considered novel potential targets for antidepressant treatment.

Wnt/ß-Catenin pathway. Several intracellular processes such as neural differentiation [63], hippocampal formation [64 65], dendritic morphogenesis [66 67], axon guidance [68 69], synapse formation [70], spatial learning [71], and memory, including long-term potentiation (LTP), seem to be regulated by the Wnt/ß-catenin pathway activity [44]. Depressed patients and young subjects who died by suicide showed impairments of Wnt/ß glycogen synthase kinase-3beta (GSK-3ß) signaling as well as a significant decrease of ß-catenin expression in the prefrontal cortex. Interestingly, antidepressant medications and mood stablizers such as valproate, lithium, and antipsychotic drugs have been reported to control both GSK-3 ß and ß-catenin expression [72-78]. These compounds may induce antidepressant-like effects or reduce anxiety by inhibiting GSK-3ß, thus enhancing brain ßcatenin levels [74 79-82]. GSK-3ß knock-in mice demonstrated impairment of cell proliferation throughout the subgranular zone (SGZ) of the dentate gyrus, a significant reduction of VEGF levels, and impaired neurogenesis in response to antidepressant drugs [83]. The antidepressant-induced ß-catenin increase has been observed in the SGZ of the dentate gyrus, both in membrane and nuclear fractions [76 84]. However, there might be a complex interaction between the GSK-3 ß-catenin pathway and other neurotransmitters which are implicated at complex levels in the pathophysiology of MDD.

As recently suggested by Pilar-Cuéllar and colleagues [44], the pharmacological modulation of the Wnt/ßcatenin pathway will presumably represent one of the most innovative mechanisms for the treatment of neuropsychiatric disorders in the next future (e.g. by block of GSK-3).

mTOR pathway. Rapamycin (TOR) genes are members of the phosphoinositol kinase-related kinase (PIKK) family of kinases [85]. mTOR-signaling pathway is involved in intracellular processes such as synaptic plasticity, memory retention, and modulation of neuronal repair after injury [44]. mTOR-signaling pathway can exist in two complexes – complex 1 (mTORC1) and complex 2 (mTORC2), depending on the presence of regulatory-associated protein of mTOR or rapamycin independent companion of mTOR, respectively [86,87]. In neurons, mTORC1 is switched on by phosphorylation in response to various neurotrophins such as BDNF. It has been suggested that the mTOR pathway is crucial for the regulation of synaptic plasticity [88]. Reductions of synaptic proteins and impairment of mTOR signaling were observed in the prefrontal cortex of depressed individuals [89] demonstrating its important role in the pathogenesis of MDD. Existing evidence [90-92] reported that mTOR, which is phosphorylated by Akt and extracellular-regulated kinase (ERK), enables the translation of synaptic protein by activating p70S6 kinase (S6K) and inhibiting 4E-BPs, the inhibitory 4E binding proteins. It is important to mention that the mTOR-signaling pathway is activated after the acute administration of different NMDA receptor antagonists such as ketamine [92], Ro 25-6981 [93], MK-801 [94], or antagonists of the group II metabotropic glutamate receptors (mGlu2/3) such as MGS0039 and LY341495. All these compounds are characterized by rapid antidepressant effects [95 96]. Some authors [92 97] suggested that the ketamine-induced synaptogenesis appears to be consequent to the blocking of NMDA receptors at rest, resulting in the translation of rapid dendritic proteins and BDNF. Ketamine rapidly activates the mTOR pathway, enhances synapse formation, increases spine synapses density in the prefrontal cortex of rats [93 98], but also increases BDNF expression in the hippocampus [99] leading to rapid antidepressant-like effects in humans [100 101] and rats [93]. The role of mTORC1 in the efficacy of ketamine was demonstrated by studies showing that pretreatment with a selective mTORC1 inhibitor such as rapamycin is able to drastically reduce the behavioral effects of ketamine [93 96]. In addition, the mTOR inhibition by rapamycin blocks ketamine-induced synaptogenesis [93]. However, mTORC2 is also supposed to play a role in ketamine antidepressant effect as it activates Akt and is involved in the organization of the actin cytoskeleton [102]. Moreover, scopolamine (for more details see below), a muscarinic receptor antagonist able to induce rapid antidepressant effects, also augments mTORC1 and leads to enhanced synaptogenesis in the prefrontal cortex [103]. Interestingly, electroconvulsive treatment has been suggested to activate the mTOR pathway inducing a VEGF enhancement [104].

In conclusion, the modulation of mTOR is a novel target for alternative therapeutic strategies for patients suffering from psychiatric disorders, in particular MDD [105].

The inflammatory hypothesis of depression: antidepressant effects of anti-inflammatory compounds

Immune alterations are considered among the most relevant mechanisms involved in the pathophysiology of depression. Several lines of evidence has led to develop the inflammatory hypothesis of depression. First, a wealth of studies showed that serum levels of proinflammatory cytokines such as IL-1, IL6, and TNF-α are abnormally increased among depressed individuals [106 107]. Furthermore, increases of pro-inflammatory cytokines seem to be linked with the occurrence of depressive-like symptoms such as sickness behavior, fatigue, lethargy, appetite loss [108]. Whereas, Infliximab, or Etanercept administration, by neutralizing TNFα and IL-1 are also associated with antidepressant effects [44 109-112]. To further demonstrate this assumption, the repression of the purinergic 2X7 (P2X7) receptor, that activates the IL-1 release, is also associated with antidepressant effects [111].

However, it is still unclear whether proinflammatory cytokines may play a role in neuronal atrophy, although preliminary data seem to support this assumption [113]. Chronic stress reduces plasmatic BDNF levels in the hippocampal dentate gyrus and increases IL-1β, IL-6, tumor necrosis factor (TNFα). Stress hormones such as cortisol, corticotropin-releasing-hormone (CRH), and adrenocorticotropic hormone (ACTH) levels contribute to cognitive impairment observed after chronic stress exposure [114]. Peripheral inflammation increases proinflammatory cytokines in the CNS that, on in turn, may control neurotransmission [115], neurotransmitter metabolism [116 117] and neurogenesis in the CNS [118 119] (for more details see) [120]. Importantly, selective serotonin reuptake inhibitors are linked with a balance of plasmatic inflammatory cytokine levels [121] while treatment-resistant depressed patients

have increased plasmatic cytokine levels compared to remitted patients [122 123]. Lastly, a higher incidence of depression among patients with chronic inflammatory diseases further supports the inflammatory hypothesis of depression [124].

Interestingly, brain expression of IDO (an enzyme that converts tryptophan into kynurenine and quinolinic acid in microglia or kynurenic acid in astrocytes) is normally low but can be significantly induced by inflammatory cytokines. Lipopolysaccharide (LPS) administration induces depression-like effects in rodents, likely via NMDA receptor agonism by quinolinic acid (IDO-dependent) [125]. IDO activation is associated with a depletion of the precursor for serotonin by increasing the degradation of tryptophan [125 126]. Microglia is activated under stress, resulting in proinflammatory state (reviewed in) [127]. Conversely, chronic stress commonly reduces both the number and size of microglia, particularly in the hippocampus [128]. Furthermore, neurogenesis in the hippocampal dentate gyrus has been reported to be significantly impaired after long-term inflammatory nociception. Significant activators of the nociception-like neurokinin 1 (NK-1) receptor and BDNF in the limbic areas have been closely associated with MDD. Interestingly, imipramine inhibits pain- and stress-evoked down-regulation of hippocampal NK-1 receptor and BDNF gene expression in rats [129]. Thus, antidepressant medications seem to block those changes, which were induced in gene expression, contributing to long-term nociceptive sensory plasticity both in the spinal cord and limbic regions implicated in mood regulation.

It has been suggested that NK-1 receptor antagonists may exert relevant anxyolitic, antidepressant, and neuroprotective effects in the CNS representing promising drugs [130]. Preliminary evidence suggests that antidepressant drugs may successfully interact with immune inflammatory signaling pathways [131]. For instance, a significant reduction of LPS-induced pro-inflammatory cytokines such as TNF-α and IL-6 and cytokine induced depressive-like behavior has been reported with antidepressant drugs use [132 133].

According to animal studies, desipramine administration has been associated with increased IL-1β mRNA levels in rat hypothalamus [134], while a significant up-regulation of phospholipase A2 (PLA2)-mediated arachidonic acid turnover has been observed after chronic antidepressant treatment in the rodent brain [135 136]. It is also important to note that resistance to commonly used antidepressants has been linked with higher levels of IL-6 and C Reactive Protein (CRP) [137 138].

Adjunctive treatment with celecoxib, a selective COX-2 inhibitor, enhanced the therapeutic efficacy of reboxetine (a noradrenergic reuptake inhibitor) in subjects with MDD [139 140]. Thus, adjunctive treatment with antiinflammatory compounds may enhance the potential of traditional antidepressant drugs. Mendlewicz and colleagues [141] found higher remission rates among MDD subjects who were previously nonresponsive to fluoxetine alone when acetylsalicylic acid (aspirin), a COX-1 inhibitor, was added to treatment. In MDD patients, adjunctive long-chain omega-3 fatty acids were associated with higher therapeutic efficacy of fluoxetine [142] and citalopram [143], respectively. Moreover, Peet and Horrobin [144] reported a significant reduction of MDD symptom severity in depressed patients who were refractory to conventional antidepressant medications.

Overall, abnormally elevated immune-inflammatory signaling represents a pathogenic mechanism contributing to mood dysregulation in MDD; therefore, altered inflammatory pathways need to be carefully considered as new targets for novel antidepressant treatments.

Other potential therapeutic targets for the development of novel antidepressants in the serotonergic system?

Serotonin or 5-hydroxytryptamine (5-HT) may be generally found in the serotonergic neurons of the raphe nuclei and their axonal projections [145]. Serotonergic transmission regulates a wide range of behaviors like mood, memory, sleep, appetite, aggression, and thermoregulation. Notably, serotonin is also involved in the modulation of hippocampal neurogenesis which is known to be abnormally impaired in both chronic stress and MDD. Administration of selective 5-HT1A and 5-HT2C receptor agonists was able to increase the number of newly formed neurons in the hippocampal dentate gyrus and/or olfactory bulb. Furthermore, stimulation of 5-HT1A and -2B receptors resulted in enhanced neurogenesis combined with antidepressant-like activity in the animal model. In order to identify novel therapeutic targets, an alternative antidepressant approach would consist in the administration of selective 5-HT1A or 5-HT2C receptor agonists that have shown specific anxiolytic/antidepressant properties based on animal models [146-148]. In addition, it has been proposed that the stimulation of postsynaptic 5-HT1A receptors in the corticolimbic brain regions is related with antidepressant effects

whereas the activation of presynaptic 5-HT1A receptors is linked with a higher propensity to major affective disorders, reduced response to antidepressants, and suicidal behavior. Chronic antidepressant treatment is linked with a desensitization of presynaptic 5-HT1A receptors drastically reducing the negative feedback related with these receptors [149]. Moreover, the combination of 5HT2C antagonism with MT1 and MT2 melatonergic agonism (e.g., the mechanism of action of agomelatine) was shown to be effective in the treatment of MDD [150]. Overall, 5-HT1A or 5-HT2C receptor agonists may provide an interesting alternative target for the treatment of MDD and need to be further implemented in the next future.

Dopaminergic and norepinephrinergic systems are highly involved in hippocampal neurogenesis. Dopamine reduction has been reported to abnormally reduce hippocampal cell proliferation [151] as demonstrated after quinpirole administration, which was associated with subgranular zone proliferation provoked by D2 receptor stimulation [152], as well as following D3 receptor knockout or inhibition [153]. According to Guiard et al. [154], the effect of dopamine on hippocampal neurogenesis is indirectly mediated by 5-HT, norepinephrine, and other neurotransmitters suggesting the complex interaction between monoaminergic systems at this level. Norepinephrine might influence hippocampal neurogenesis, considering the extensive noradrenergic innervation of the adult hippocampus. Importantly, the norepinephrine depletion was found to weaken the proliferation, but not survival/differentiation of adult hippocampal granule cell progenitors [155]. Given this context, the authors suggested that the hippocampal precursors of neurogenesis might be modified through the α- adrenergic receptor activity [156 157] although their functioning still remained unclear [158]. Alpha-2-adrenoceptors are identified as presumed targets in the development of rapid acting antidepressants [8]. Various studies demonstrated increased α2-adrenoceptor expression as well as binding and functional actions within limbic brain areas in both patients with major depression and animal models of depression [159-162]. Chronic antidepressant treatment has been found to down-regulate and desensitize α2-adrenoreceptors, therefore proposed to mediate the therapeutic delay of antidepressant medications [163 164]. Antidepressant drugs with α2-adrenoceptor antagonist properties, such as mirtazapine, are associated with more rapid behavioral effects, alone or in combination with other traditional antidepressants[165,166]. Interestingly, the co-administration of α2-adrenoceptor antagonist yohimbine with fluoxetine [167] or the tricyclic antidepressant imipramine [168] hastens the antidepressant response in patients with MDD. Therefore, antagonism of the α2-adrenoceptor may be identified as a prospective target in the development of antidepressant monotherapy or combined antidepressant treatment [169].

Similarly to antidepressants, cannabinoids may also reduce anxiety and depressive symptoms in the short term [32 170]. Chronic antidepressant treatment with SSRIs and tricyclics was reported to alter the expression of cannabinoid (CB1) receptors and endocannabinoid levels (EC) in brain regions involved in the pathophysiology of mood and anxiety symptoms [59 74 171-174]. Genetic or pharmacological manipulations of both CB1 and CB2 or enzymes involved in the endocannabinoid metabolism also regulates hippocampal neurogenesis: thus, disruption of endocannabinoid signaling could be involved in the reduction of hippocampal neurogenesis induced by chronic stress. Notably, cannabinoids can also impact on serotonergic neurotransmission and serotonin 1A and 2A/2C receptors expression [175 176]. A better understanding of this complex interaction may contribute to the development of new targets in the treatment of mood and anxiety disorders [177].

It is now becoming evident that the normalization of hippocampal neurogenesis caused by antidepressants may be associated with the glucocorticoid hormones [7 178-180]. Fitzsimons et al. [181] reported that antiglucocorticoids might revert depressive symptoms by promoting neurogenesis in the ventral hippocampus. Mice that are heterozygous for glucocorticoid receptor (GR) showed a depression-related phenotype, that is, elevated learned helplessness on the behavioral level and neuroendocrine alterations with HPA axis overdrive. Moreover, they had abnormally impaired BDNF levels and altered neurogenesis further repressed by restraint stress [182]. Traditional antidepressants are known to modulate GR activity [7 183 184] as they might affect neuroplasticity through their potential to modulate both BDNF and 5-HT, potentially influencing HPA axis, which is subsequently able to affect hippocampal neurogenesis and neuronal functioning [185]. Moreover, the antidepressant effects of chronic fluoxetine treatment were described to be linked to the maturation of newborn neurons together with the HPA axis inhibition [186]. The down-regulation of hippocampal neurogenesis may affect HPA axis functions observed in chronic stress or depressed patients [186 187]. In addition, the normalization of stress related HPA axis abnormalities following pharmacological inhibition of the orexinergic system was con-

nected with antidepressant effects [188]. Thus, another potential class of medications with antidepressant action could be anti-glucocorticoid treatments which are reported to diminish stress-induced depressive symptoms by increasing neurogenesis [189].

Estrogens (the estrogen receptors (ER) α and β) might regulate synaptogenesis and dendrite length, also activating intracellular signaling pathways that control the formation of synapse, and cause antidepressant effects in behavioral models of depression [190 191]. Clinical studies reported the neuroprotective effects of estrogens against cognitive decline during normal aging but also Alzheimer's symptoms, whereas laboratory evidence provided insight into the mechanisms through which estrogens may induce changes in brain neuroplasticity. Specifically, electrophysiological studies suggested that estrogens are able to promote changes in synaptic plasticity within the central nervous system. New selective estrogen ligands showed an advantageous potential reversing the effects of chronic stress such as atrophy of neurons as well as several behavioral symptoms of depression [192 193].

As a whole, the 17β-estradiol-mediated neuroprotection has been characterized by initial studies but there is an urgent need to elucidate the impact of estrogens on different signaling pathways involved in the regulation of cell survival and death.

Vilazodone, vortioxetine, brexpiprazole (OPC-34712), and amitifadine

Vilazodone acts by inhibiting serotonin reuptake and by partial agonism of 5-HT1A receptors [194]. It has been approved as antidepressant by the US Food and Drug Administration in 2011. Importantly, 5-HT1A partial agonism has been associated with the improvement of depressive, anxiety [195], and aggressive [196] symptoms. According to clinical studies, vilazodone at 40 mg daily dose is associated with a significant antidepressant response as demonstrated by the improvements at the MADRS and HAMD-17 total scores after one week of treatment [197] and a significantly higher response rate than placebo at week 8 based on MADRS total score [198]. Vilazodone has demonstrated a good tolerability profile similar to that observed with SSRIs with diarrhoea, nausea, and somnolence [198] as the most relevant treatment-emergent adverse events.

Similarly, vortioxetine acts as a partial agonist at the 5-HT1A receptor, and a SERT, HT3, and 5-HT7 inhibitor [199]. It has been recently approved in Italy for the treatment of major depression. The antagonistic effects on 5-HT7 receptors of this drug are associated with improvements of sleep, circadian rhythms, and mood. Based on preclinical studies, vortioxetine has been associated with a more pronounced and rapid recovery of 5-HT neuronal firing when compared with other SSRIs. When compared with placebo, vortioxetine was associated with significant improvements from baseline to week 6 in the mean change of MADRS total score in a sample of 429 patients with severe MDD. Alvarez and colleagues [200] reported significant and earlier improvements vs. placebo according to HAMD-24 total scores for both 5 and 10 mg daily doses of this medication from week 1 (when compared with venlafaxine from week 2). A better tolerability profile when compared with that of 225 mg venlafaxine was also observed [200].

Brexpiprazole (OPC-34712) is a novel promising medication for the treatment of MDD, with similar structural characteristics and pharmacological properties to aripiprazole. Brexpiprazole has a broader activity across multiple monoamine systems, reduced partial agonism on D2 receptors, and enhanced affinity for 5-HT1A, 5-HT2A and 5-HT7 receptors. It has been proposed as an adjunctive treatment in MDD. Relative to placebo, brexpiprazole as adjunctive treatment has been associated with significant improvements on MADRS total score in patients with insufficient response to other antidepressants.

Furthermore, amitifadine (DOV 21,947)/DOV-216,303 amitifadine (previously DOV 21,947) and DOV 216,303 (a racemic mixture of which amitifadine is one of the enantiomers) are other two interesting molecules currently under development to treat MDD. Both are serotonin-NE-dopamine reuptake inhibitors and promising therapeutic options, although prior trials on other triple-reuptake inhibitors such as SEP225289 (Sepracor Inc., 2009) and GSK372475 had yielded conflicting results [201]. However, amitifadine is a serotonin preferring triple-reuptake inhibitor with lower affinity for the dopamine transporters, differently from SEP225289 and GSK372475. Such differences in the relative affinities for the three transporters may explain the improvements in pharmacology, tolerability, and efficacy observed in the earliest studies for these novel compounds. Amitifadine has been associated with markedly and persistently increases in extracellular concentrations of serotonin, noradrenaline, and dopamine in the prefrontal cortex [202]. Time-dependent significant reductions in HAMD scores were observed both with DOV 216,303 and citalopram [203]. Based on a post-hoc analyses,

amitifadine was reported to be particularly effective for anhedonia and did not exert significant sexual side-effects or other serious adverse events over 6 weeks [204].

Rapid acting antidepressant effects: the potential of glutamatergic compounds

Modern antidepressant medications may work by reversing neuroplasticity impairments associated with chronic stress and MDD and restoring the abnormal changes observed in specific neural circuits [48 52 54 205]. Although conventional antidepressants predominantly modulate norepinephrine, dopamine, and/or 5-HT systems [206], the interest towards glutamatergic system is growing in terms of importance [43]. It is well established that the majority of molecular and biological impairments of neuroplasticity are associated with the cytotoxic action of glutamate. For instance, the antidepressant-mediated inhibition of stress-induced morphological changes in both the hippocampus and amygdala is dependent on glutamatergic transmission [207]. In addition, according to animal models stress-induced morphological changes in the hippocampus are reversed by pharmacological manipulation of glutamatergic system [207 208].

Importantly, a critical role of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptors activation in inducing morphological changes associated with neuroplasticity such as reduction of dendritic length and branching, spine density, and hippocampal volume has been suggested by multiple evidence [209 210]. NMDA receptors are composed by two major subunits, NR1 and NR2 as functional NMDA receptors are tetramers and are comprised of two NR1 subunits and two NR2 subunits. NR2b subtype may be commonly found in extrasynaptic locations and has been explored as a new target for blocking glutamate excitoxicity damage [211]. NR2b antagonists may show antidepressant effects exerting antidepressant-like activity similarly to ketamine (for more details see below) but without exerting significant adverse effects [192 193]. The structural remodeling of neurons leading to reversible modifications such as reduced neurogenesis, neuronal shrinkage and decreased growth may be, at least partially, mediated by glutamate if present at certain concentrations as well as by glucocorticoids levels [212]. The inhibition of glutamate release by NMDA receptors may prevent this structural remodeling [213 214].

Both antidepressants and electroconvulsive shock therapy can reverse glutamate impairment, particularly in the anterior cingulated cortex of subjects with MDD [215]. The antidepressant tianeptine has been reported to prevent the retraction of hippocampal CA3 pyramidal neurons apical dendrites together with increasing granule cell proliferation [49]. Differently from fluoxetine, tianeptine prevents an excessive release of glutamate in the basolateral nucleus of the amygdala. NMDA receptor antagonists such as ketamine have been associated with rapid antidepressant action in TRD patients [100 216]. Ketamine may be considered as safe and well-tolerated in the short-term period for nonpsychotic depressed patients when administered at a subanesthetic dose of 0.5 mg/kg over 40 minutes as well [217]. Duncan et al. [218] reported that ketamine represent a novel and promising option to treat both MDD and TRD patients according to its earlier efficacy. It wa shown to drastically reduce depressive symptoms within the first 5 days in contrast with the delayed action of currently available antidepressant medications, requiring 4 to 6 weeks. Ketamine seems also effective in reducing suicidality among TRD patients according to its rapid onset of action on core depressive symptoms, as well as hopelessness [219]. It was suggested that (S)-ketamine is approximately 4 times more active than its (R)-enantiomer given its better pharmacokinetic properties and higher tolerability [219 220]. (S)-ketamine has also been reported to induce less psychomimetic adverse effects such as dissociation and hallucinations relative to (R)- enantiomer. Several studies showed that rapid-acting antidepressants are able to enhance glutamate transmission, mTORC1 signaling as well as synaptogenesis [103 192 193] but other relevant mechanisms need to be mentioned. The rapid induction of neuroplasticity is supposed to be one of the main mechanism underlying the antidepressant effect of ketamine [221]. Duman et al. [98] focused on the additional activity of ketamine to rapidly reverse both behavioral and neuronal changes associated with chronic stress presumably due to the stimulation of BDNF signaling. Unfortunately, ketamine has important psychotomimetic effects that may seriously limit its utility and require additional studies.

Memantine is another N-methyl-D-aspartate receptor (NMDAR) antagonist, a dimethyl derivative of amantadine. It showed good tolerability [222] and demonstrated preliminary hints of antidepressant efficacy based on animal models of depression [223]. Moryl and colleagues [224]. More specifically, memantine may be associated with antidepressant-like activity by reducing immobility time in the forced swim test. There are

also evidence suggesting that combining memantine with traditional antidepressants may be effective in the treatment of MDD. The enhanced antidepressant action may be observed only when fluoxetine was administered with memantine indicating that the combined effect of traditional antidepressants and NMDA antagonists is necessary to induce any antidepressant effects [225].

Finally, the non-selective muscarinic (M) receptor antagonist scopolamine has been also associated with a rapid antidepressant-like effect [75 226]. Scopolamine inhibits all five receptors located at pre- and postsynaptic sites and it is associated with modulation of both cholinergic and glutamatergic transmissions. It was suggested that postsynaptic M1 receptors can regulate long-term synaptic depression (LTD) through the induced AMPA/NMDA receptors internalization [227]. The inhibition of these receptors induced by scopolamine is associated with enhancing synaptic plasticity and synaptogenesis suggesting that this medication may determine the inhibition of muscarinic activation of GABA firing as well as the dis-inhibition of glutamate release [192].

The possible role of miRNAS

Finally, a further alternative antidepressant strategy needs to be reported. MicroRNAs (miRNAs), which regulate gene expression by targeting the three prime untranslated region (3′-UTR) of genes, have been demonstrated to play a significant role in neurogenesis [228], thus they may need to be considered as new targets in the treatment of major neuropsychiatric conditions [216 229 230]. Exploring miRNAs effects may help to develop new molecular strategies aimed at modulating the expression of certain genes with an interesting potential in the antidepressant field [231]. To date, more studies are still required to thoroughly explore the specific role of miRNAs in depression-related disorders as well as investigate detailed information about the possible use of miRNAs as new therapeutic targets for antidepressant activity.

Conclusion

The present review examined the main novelties in the field of antidepressant pharmacology, by including a brief overview of novel agents and potential innovative molecular targets with their implications and future perspectives. Over the last 20 years, the theoretical landscape has radically changed: the classic serotonergic view of depression has been integrated with substantial knowledge on other monoamines and specific intracellular signaling pathways. In addition to 5-HT, dopaminergic and norepinephrinergic systems, neurotrophic factors play a fundamental role in neuronal growth, differentiation, and survival, while neuroplasticity is now recognized as a crucial factor in the pathogenesis of depression. Furthermore, several intracellular pathways (e.g., cyclic adenosine monophosphate pathway, Wnt/ß-Catenin Pathway, and mTOR pathway) may function as final common mechanisms for these systems. Thus, the direct modulation of intracellular pathways represents an exciting perspective for novel treatment strategies in MDD.

Current models of depression have recognized a prominent role also to other pathophysiological mechanisms, such as neuro-inflammation and chronic stress, which constitute the basis for further advancement in the field of psychopharmacology. Immune/inflammatory abnormalities have been also hypothesized to be involved in the pathophysiology of major depression and medications associated with a reduction of neuroinflammation represent innovative options in the treatment of MDD. Indeed, part of the clinical efficacy of current antidepressant medications may already work by reducing immune inflammatory signaling pathways; thus, altered inflammatory pathways need to be carefully considered as novel alternative targets for developing novel antidepressant treatments. Estrogen ligands are an additional endocrine target, currently in the early phase of development. Selective agonists have been proposed to reverse the effects of chronic stress such as atrophy of neurons as well as several behavioral symptoms of depression. Similarly, molecules that target the cannabinoid system may also reduce anxiety and depressive symptoms and are potential targets for novel antidepressants.

Glutamate transmission is already targeted by novel antidepressants. Drugs targeting specific glutamate receptors have been already marketed after demonstration of their efficacy [4]. The noncompetitive NMDA receptor antagonist ketamine has been identified as one the most intriguing therapeutic option for patients with MDD and TRD. Ketamine is associated with a rapid and prolonged glutamate burst stimulating the BDNF-mTORC1 cascade, and leads to increased synaptic connections in specific brain areas such as the prefrontal cortex [232]. The acute synaptogenic action of ketamine is rapid and is not associated with excitoxicity. However, future studies are required to test long-term clinical efficacy in both MDD and TRD.

The efficacy of scopolamine, a muscarinic agent, largely depends on glutamate transmission, and also showed rapid effects.

Despite these exciting perspectives in the field of antidepressant drug discovery, clinicians continue to be challenged by the need to manage MDD while addressing several unmet needs in terms of tolerability, efficacy and long-term acceptability. Thus, further studies are urgently needed to translate preliminary evidence into tangible advances for our patients.

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None

Take home messages for psychiatric care

- Over the last 20 years, the classic serotonergic view of depression has been significantly integrated with substantial knowledge related to the contribution of other monoamines and specific intracellular signaling pathways
- In addition to 5-HT, dopaminergic and norepinephrinergic systems, neurotrophic factors play a fundamental role in neuronal growth, differentiation, and survival. Modern antidepressant drugs such as ketamine may act by reversing neuroplasticity impairments and enhance synaptogenesis
- Immune/inflammatory abnormalities have been suggested to be involved in the pathophysiology of major depression and medications associated with a reduction of neuroinflammation represent innovative options in the treatment of major depression

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