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Contents

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Cognitive deficits and psychosocial functioning in schizophrenia: role of computer-assisted cognitive remediation

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Summary

Objective. The aim of this study was to evaluate the effectiveness of a computer-assisted cognitive remediation program (CACR) (through the use of the Cogpack software) on cognitive outcomes, symptomatology, and real-world functioning compared to a control active group following 24 weeks of treatment in a sample of outpatients with stable schizophrenia.

Materials and methods. Forty-four outpatients took part in the study: twenty-three of them were allocated to CACR and twenty-one to the control active group. First, we calculated chi-square tests for categorical variables and the univariate analysis of variance (one-way ANOVA) analyses of variance for continuous variables. Second, an ANOVA for repeated measures was performed for clinical and psychosocial variables.

Results. A significant improvement over trial duration (within-group effect) was observed for both treatments in positive (PANSS-P), negative (PANSS-N), general symptoms (PANSS-G), and verbal learning (HVLT-R). CACR was found superior to the control active group (between group effect) in improving specific cognitive domains: processing speed (TMT, BACS, fluency); verbal learning (HVLT-R); reasoning and problem solving (NAB); visual learning (BVMT-R); attention/vigilance (CPT-IP); social cognition (MSCEIT-ME); social acceptability (SLOF social acceptability). No differences were found between groups for the other clinical outcomes' measures.

Conclusions. Our data suggest that the use of CACR is important to implement not only specific cognitive functions, but also functioning in daily life and social cognition in patients with stable schizophrenia.

Introduction

Cognitive deficits have been considered a nuclear feature of schizophrenia: they are already present at the onset of the disorder, but also in the prodromal phase and tend to be stable over time. The impairment of cognitive performance is, on average, two standard deviations below healthy controls [1] and only 15-30% of patients are not deficient in neuropsychological tests, despite having a reduced cognitive functioning based on the premorbid level and the level of parental education [2]. Cognitive deficits are the most important determinant in the impairment of the daily functioning of patients with schizophrenia: they explain, globally, from 20 to 60% of the variance of functioning, with differences ascribable to the heterogeneity of the samples and the evaluation tools adopted [3 4]. An impairment in cognitive domains such as processing speed, attention, episodic memory, working memory and executive functions is strongly associated with poorer psychosocial functioning, including quality of social relationships, role functioning, self-care skills, and independent living [5 6].

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Moreover, cognitive impairment attenuates response to psychiatric rehabilitation, such as supported employment and social skills training [7].
To treat cognitive deficits and, later, act on the functioning of patients with schizophrenia, cognitive remediation (CR) methods have been developed and evaluated [8]. The most common of these methods include strategy coaching to improve performance on cognitive exercises, teaching cognitive compensatory (or self-management) strategies to reduce the effects of impaired cognitive functioning in everyday life, and drill-and-practice of cognitive exercises [9]. The goal of strategic training is to improve performance by explicitly learning and applying cognitive strategies, such as mnemonics [10].
On the other hand, the principle of drill and practice training has been adopted in the design of computer-assisted cognitive remediation CR programs (CACR) for patients with schizophrenia-spectrum disorders (e.g. CogPack and CogRehab). These computer programs are flexible and have several advantages over the pen and pencil programs, such as the enhancement of motivation due to the sensory variety that these exercises present [11 12], and the possibility of providing immediate feedback [13]. Other important features of CACR are its presentation of custom-tailored and adaptive tasks that can take into account the patient's deficits and their evolution over the course of therapy (specific sets of exercises can be individualized for the individual cognitive functions in which the patient is deficient, it is possible to modulate the difficulty based on individual answers) [14], standardization of instructions, and the possibility to perform the training with only little help from therapist, thereby containing costs [15].
However, evidence for the efficacy of such programs in improving (cognitive) functioning remains unclear.
Three meta-analyses including both drill and practice and strategic training and coaching showed that CR in general was effective in a broader sense on cognitive functioning in patients with schizophrenia-spectrum disorders [10 16 17]. More specifically, Wykes et al. (2011) showed that both drill and practice and strategic training improved cognitive outcomes; McGurk et al. (2007) found a larger effect on verbal learning and memory for drill and practice training alone, rather than combined with strategic training. Lastly, Grynszpan et al. (2011) performed a meta-analysis on 16 randomized controlled trials evaluating CACR and showed positive results on general cognition, with small effect sizes on verbal memory, working memory, attention/vigilance and speed of processing and a significant medium effect size for social cognition. Interestingly, cognitive domains that were specifically targeted by the interventions did not yield higher effects than those that were not, suggesting a "non-specific" effect of CACR.
A more recent metanalysis [11] including 24 studies specifically focused on computerized drill and practice programs showed that computerized cognitive training had a superior effect on attention and working memory, as well as on positive and depressive symptoms, when compared to a control condition. Furthermore, small to moderate, but only marginally significant effects were found for processing speed, verbal fluency, and verbal and visual learning and memory. No convincing evidence for improvement in general cognition, reasoning and problem solving, social cognition, and functional outcomes has emerged. Moreover, while longer illness duration was related to larger effect sizes for attention, shorter treatment duration was related to higher effect sizes on working memory and visual and verbal learning and memory. Thus, the dubious effects on social cognition and functional outcomes questions the generalization of cognitive improvement to other domains.
Therefore, in light of these considerations and the growing interest in CR programs, the objective of the present study was to evaluate, in a sample of outpatients with schizophrenia, the effectiveness of a CR program (through the use of the Cogpack software) in addition to standard therapy on cognitive outcomes compared to a control active group and to highlight a possible effect on symptomatology and real-world functioning.

Materials and methods

Subjects

The present study was conducted at the Dipartimento di Neuroscienze "Rita Levi Montalcini", Università degli Studi di Torino, Dipartimento di Neuroscienze e Salute Mentale, Struttura Semplice Dipartimentale Coordinamento Assistenziale Psichiatrico Ospedale-Territorio, AOU Città della Salute e della Scienza - Presidio Molinette, Torino, Italy and the Dipartimento Interaziendale di Salute Mentale ASL TO3 & AOU San Luigi Gonzaga, Italy, in the period between October 2017 e March 2019. Patients, initially evaluated by a psychiatrist, if they met the DSM-5 criteria for diagnosis of schizophrenia, were subsequently visited by our research group. The patients examined were aged between 18 and 65 years. The study was conducted on a sample of outpatients with diagnosis of schizophrenia in stable phase of illness.
The exclusion criteria were the following: a) co-presence of a diagnosis of intellectual disability and learning disabilities; b) hospitalization in psychiatric facilities in the six months prior to evaluation, and significant change of antipsychotic medications during the previous three months (according to clinical judgement).
Participants were recruited through referrals from attending psychiatrists or clinical staff at the psychiatric medical facilities where the study was conducted.
Written informed consent was obtained from all subjects after a complete description of the study. All patients were submitted to standard care provided in community mental health centers in Italy (pharmacological treatment, clinical monitoring at least on a monthly basis, home care when required).

Interventions

All patients recruited in the trial were allocated to one of the two interventions, computer-assisted CACR (Cogpack) and control active group.
In this trial, patients were considered completers if they attended at least 80% of the planned sessions.

Control active group

This condition was designed to control for nonspecific treatment effects. It specified an equal number of one-on-one computer sessions with the same trainers who conducted the CACR sessions, using the same schedule as the treatment arm: two-hour biweekly sessions. It offered supportive trainer interactions and matched experience with computers and varied computer activities. Control activities were selected for game-like properties and low cognitive demand. Participants in this condition did not receive problem-solving training or guided practice on the exercises used in the remediation condition. The control sessions were also videotaped and reviewed in supervision meetings.

Cognitive remediation group

The CACR group received 48 sessions computerized rehabilitation using Cogpack software, performed twice weekly, for a total of 24 weeks of treatment, in addition to standard therapy.
Cogpack is a computer-assisted cognitive remedy that requires the use of different abilities, including: visuomotor speed, understanding, concentration, alertness, language, memory and other cognitive functions. The exercises are grouped according to the cognitive domains that are tested: visuomotor skills, vigilance, language, memory, logic and calculations, daily skills, culture and special element orientation. The Cogpack software includes 64 different tests that can be composed to generate 540 different rehabilitation programs, so that it is possible to personalize the rehabilitation adapting it to the neuropsychological deficit found in the patient. Based on the results obtained by the patients in the previous tests, the exercises can be modulated in a programmed way or self-modulated by the software itself so that it can always improve individual performance. The variability of the exercises in the same category also makes it possible to rehabilitate the same neurocognitive function by using new tasks as soon as the patient manages to solve all the levels of the same exercise. The therapist has a fundamental role, because he allows learning without errors (as the patient with schizophrenia shows poor learning and trial skills); he must also set the initial level of the task to allow greater chances of success and finally he must not miss a continuous positive reinforcement that helps the patient to understand the reasons of possible failures and to improve himself. We also conducted a weekly group session designed to promote the transfer of improved cognitive functioning to real-world situations. The trained therapists also provided participants teaching compensation strategy or prompting additional practice if needed.
Additionally, at least one therapist at each site had to take 1-day training course to learn the CACR program before the study was started. Therapists involved in the intervention were psychologists, and technicians of psychiatric rehabilitation who were familiar with psychiatric rehabilitation for schizophrenia, and supervised during the study period by members of the research team who had several years of experience with CR. Internet conferences between members of the research team were also held during the study period. Using computer software and the manual also minimizes the disparity of efficacy in cognitive remediation.
In the CACR training, participants were directed to practice a wide range of cognitive domains in both the early and later phases of remediation, and each participant could choose either preferable tasks or unskilled tasks to enhance their interests or self-efficacy in the later phase. In the groups, participants talked about their weak tasks, and discussed with each other strategies to complete tasks using some cognitive functioning in the early phase. In the middle and later phases, they also discussed social goals and how to transfer gained cognitive skills to achieve their goals.
The trial was carried out in accordance with the Declaration of Helsinki of 1995 (as revised in Edinburgh in 2000) and was approved by the Local Ethical Committee.
Patients were evaluated using a semi-structured interview to assess demographic and clinical features. Data were collected to determine age, gender, years of education, status of employment, marriage or an equivalent long-term relationship, length of illness, number of hospitalizations and antipsychotic treatment.

Psychiatric assessment

All subjects were evaluated at baseline (T0) and after six months (T1) with the following evaluation instruments: the *Positive and Negative Syndrome Scale* (PANSS); The *Calgary Depression Scale for Schizophrenia* (CDSS); the *MATRICS Consensus Cognitive Battery* (MCCB); the *Specific Levels of Functioning Scale* (SLOF).
Current levels of psychopathological symptoms were assessed using the PANSS, which includes positive symptoms (PANSS-P), negative symptoms (PANSS-N), and general psychopathology (PANSS-G) subscales. The CDSS was used to measure depressive symptoms [18].
Neurocognition was measured according to the 7 cognitive domains of the MCCB [19-21], derived from scores on 10 cognitive measures: speed of processing (*Trail Making Test Part A*; *Brief Assessment of Cognition in Schizophrenia*: Symbol Coding; *Category Fluency Test*: animal naming), attention/vigilance (*Continuous Performance Test*: Identical Pairs), working memory (*Wechsler Memory Scale*; spatial span subset; *Letter Number Span Test*), verbal learning (refers to immediate verbal memory, *Hopkins Verbal Learning Test (HVLT)-Revised,* immediate recall), visual learning (refers to immediate visual memory, *Brief Visuospatial Memory Test-Revised*), reasoning and problem solving (*Neuropsychological Assessment Battery* (NAB), mazes subtest).
The assessment of SC included a test contained in the MCCB: the *Mayer Salovey Caruso Emotional Intelligence Test* (MSCEIT) [22], managing emotion section, which examines the regulation of emotions in oneself and in one's relationships with others by presenting vignettes of various situations, along with ways to cope with the emotions depicted in these vignettes. It was integrated by the *Facial Emotion Identification Test* (FEIT) [23], which examines emotion perception, and *The Awareness of Social Inference Test* (TASIT) [24], which is a TOM test consisting of

7 scales (positive emotions, negative emotions, sincere, simple sarcasm, paradoxical sarcasm, sarcasm enriched, lie), organized into three sections: Emotion Recognition; Social Inference (minimal); Social Inference (enriched). The manual of the TASIT was translated into Italian by a psychiatrist of the Department of Psychiatry of the University of Campania "Luigi Vanvitelli", Naples, who gained experience in the use of the English version of the instrument during his stage at the Department of Psychiatry and Biobehavioral Sciences at University of California, Los Angeles (UCLA), as part of his PhD Course. The videotaped vignettes of the TASIT were dubbed in Italian at the Fono Roma Studios (www.fonoroma.com), a prestigious society in the field of film industry. As to the FEIT, the adaptation of the Italian version required the translations of the six emotions reported on the screen above the stimuli.
Real-life functioning was measured using the SLOF [25-27]. The original SLOF is a 43-item self- or informant-rated scale of a person's behavior and functioning which was abbreviated to assess the following domains: Interpersonal Functioning (e.g. initiating, accepting and maintaining social contacts; effectively communicating), Independent participation in Everyday Activities (shopping, using telephone, paying bills, use of leisure time, use of public transportation), and Vocational Functioning (e.g. employable skills, level of supervision required to complete tasks, ability to stay on task, completes tasks, punctuality). The SLOF consists of 43 items. Each of the questions is rated on a 5-point Likert scale, indicating the level of assistance the participant needs to perform the task, with higher score indicating better functioning. Scores on the instrument range from 43 to 215. The SLOF differs from the other outcome measures in emphasizing patient's current functioning and observable behavior, as opposed to inferred mental or emotional states, and focuses on a person's skills, assets, and abilities rather than deficits that once served as the central paradigm guiding assessment and intervention for persons with disabilities. Moreover, the SLOF does not include items relevant to psychiatric symptomatology or NC dysfunctions [25 27].

Statistical analysis

Statistical analyses were performed using the Software System Statistical Package for the Social Sciences, SPSS, version 25 for Windows (SPSS, Chicago, IL, USA). Data are expressed as average and standard deviation or percentages.
Analyses were planned in two stages. In stage 1, we performed chi-square tests for categorical variables and the univariate analysis of variance (One-way ANOVA) analyses of variance for continuous variables, in order to examine whether the two groups differed in baseline socio-demographic and clinical variables.
In stage 2, an ANOVA for repeated measures was performed for clinical and psychosocial variables. The between-subject factor was the group (CACR/control active group), and the within-subject factor was time (T0; T1). Effects of time (longitudinal dimension), group (cross-sectional dimension), and time by group (interaction effect) were examined.

Results

Forty-four outpatients meeting DSM-V criteria for schizophrenia took part in the study.
Twenty-three of these patients were allocated to CACR and twenty-one of them to the control active group. Five patients dropped-out from the CACR group and six from the control active group. Therefore, the final sample included 18 patients in the CACR group and 15 subjects in the control active group. Statistical analyses were performed on patients who completed the sessions of treatment. There were no significant differences with one-way ANOVA and chi-square test in socio-demographic, cognitive, and clinical characteristics between the two treatment groups, except for age, as patients in the active control group were older than those in the CR group. In addition, the severity of symptoms at baseline measured with the PANSS was not significantly different between groups.
Socio-demographic, cognitive, and clinical variables of the two treatment groups at baseline are shown in Table I. Results of the evaluation scales for the two treatment groups at T0 and at T1 are displayed in Table II. A significant improvement over trial duration (within-group effect) was observed for both treatments in positive (PANSS-P), negative (PANSS-N), general symptoms (PANSS-G) and verbal learning (HVLT-R).
CACR was found superior to the control active group (between group effect) in improving specific cognitive domains: processing speed (TMT, BACS, Fluency); verbal learning (HVLT-R); reasoning and problem solving (NAB); visual learning (BVMT-R); attention/vigilance (CPT-IP); social cognition (MSCEIT-ME), social acceptability (SLOF Social Acceptability).
No differences were found between groups for the other clinical outcomes' measures.

Discussion

This study was aimed to assess the effectiveness of CACR versus a control active group on specific clinical and functional domains in a sample of outpatients with schizophrenia spectrum disorders. The CACR group was contrasted with an active experimental condition that controlled for nonspecific elements of the remediation training, including supportive therapist interactions and exposure to interesting computer activities. Outcomes were assessed at three levels: proximally, on the remediation training exercises; intermediately, on neuropsychological measures not involved in the training; and more distally, on proxy measures of everyday functioning. The two groups taking part in the study were well matched at baseline assessment on demographic (except for age) and clinical confounding variables (i.e. depression) that could negatively impact the outcome measures and made biased the study results.
We found that CACR and active control group can be considered both effective treatments for patients suffering from schizophrenia spectrum disorders. In fact, both interventions showed a significant and similar efficacy in improving symptomatology.
Nevertheless, some specific differences between the two

Table I. Socio-demographic, clinical, cognitive and functioning characteristics of the sample at time zero.

Variables	TAU	Cogpack	F/χ^2	p
Age (years)	42.72±8.47	36.46±7.31	5.10	.03
Sex (male*)	10	3	1.09	.30
Single*	8	2	.28	.59
Employment*	21	10	1.22	.27
Scolarity (years)	11.08±3.82	13.23±3.47	2.88	.10
Age of onset	25.68±7.49	26.54±4.21	.15	.70
Duration of illness (years)	17.04±9.88	10.00±5.18	5.73	.02
PANSS-P	15.24±6.92	11.23±3.09	3.91	.06
PANSS-N	22.00±7.11	24.31±6.96	.95	.33
PANSS-G	36.08±9.98	36.54±10.63	.02	.90
PANSS total	72.96±17.95	72.85±16.69	.00	.98
CDSS	1.80±2.04	3.46±4.27	2.66	.11
Speed of processing	24.48±9.99	27.69±9.23	.93	.34
Social cognition	27.40±10.74	28.62±6.33	.14	.71
Working memory	29.64±11.16	31.38±9.94	.36	.55
Verbal learning	33.36±8.64	34.08±8.94	.06	.81
Reasoning/problem solving	32.28±4.71	34.00±9.46	.57	.46
Visual learning	35.92±14.06	36.92±17.34	.04	.85
Attention/vigilance	28.36±9.03	34.08±11.02	2.95	.09
SLOF total	179.12±17.35	175.00±18.70	.46	.50

*Data are expressed as mean ± standard deviation. * data expressed as a number. Statistical analysis: One-way ANOVA for continuous variables; χ^2 for categorical variables.*
PANSS-P: Positive and Negative Syndrome Scale, positive symptomatology; PANSS-N: Positive and Negative Syndrome Scale, negative symptomatology; PANSS-G: Positive and Negative Syndrome Scale, general symptomatology; PANSS total: Positive and Negative Syndrome Scale, total; CDSS: Calgary Depression Scale for Schizophrenia; SLOF total: Specific Level of Functioning, general functioning.

groups were observed. In particular, the CACR therapy group presented improvements, after six months of treatment, in specific cognitive domains (processing speed, verbal learning, reasoning and problem solving, visual learning, attention/vigilance), social cognition, and social acceptability, whereas the active control group did not. Working memory remained unaffected by both treatments. Lastly, while verbal learning improved in both groups over assessment occasions, a significant time×group interaction was evident, suggesting an advantage for CACR training in this specific neurocognitive domain.

Several studies have been performed to examine the effectiveness of CACR therapy in addition to usual treatments in patients with schizophrenia and they obtained discordant results. The lack of consistent findings across studies is not surprising considering the methodological limitations of the studies published thus far [8]. Most of them have had modest sample sizes of under 60 participants receiving a particular type of cognitive remediation [28-32], and two studies combined participants receiving different types of CR [31 33]. Three studies evaluated CR interventions with as few as one [32] to ten sessions [28 29]. Moreover, CR studies are conducted on inpatients [34-36] and outpatients [37-40]. Although evidence indicates that the patient status is not of importance, it may, however, be essential for a massed treatment schedule as adherence is more difficult to ascertain in outpatients [14]. Lastly, CACR have the potential to be performed independently by the patient. Many papers did not provide sufficient information on this topic and it is not possible to assess the effect of the amount of therapist involvement on training efficacy.

The positive findings regarding the amelioration of attention and vigilance, processing speed, verbal and visual learning and reasoning and problem solving reported in the present study are in concordance with several other studies that have utilized the CACR in patients with schizophrenia [11]. Processing speed is related to the ability to carry out the activities of daily life, to the degree of independence achieved and to the ability to get a job and therefore seems to be the basis of the poor performance of other cognitive tests and the impairment of global functioning [41]. The advantage of CR for processing speed, attention/vigilance and verbal and visual learning in the present study suggests, however, that at least some additional neurocognitive benefit may derive from the careful titration of task difficulty of cognitive exercises to ensure appropriate cognitive challenge, the rapid repetition of exacting exercises, and the frequency of reinforcement associated with achievement of intermediate and overall task goals characteristic of this condition. The hierarchical nature of the training program, starting with training in elementary attention skills and then graduating to considerably more complex episodic and verbal memory tasks may also play a role in the advantage of this condition [42].

Thus, the finding of a no advantage of CACR on work-

Table II. Analysis of the variance of scores variations of clinical, cognitive and functioning evaluation scales in the two treatment groups.

	TAU	Cogpack	ANOVA within groups F (p)	ANOVA between groups F (p)
PANSS-P				
T0	15.24±6.92	11.23±3.09	**3.38 (.04)***	1.72 (.20)
T1	12.00±3.91	11.77±4.30		
PANSS-N				
T0	22.00±7.11	24.31±6.96	**5.60 (.00)***	.01 (.91)
T1	21.52± 6.47	19.31±3.33		
PANSS-G				
T0	36.08±9.98	36.54±10.63	**4.86 (.03)***	.28 (.60)
T1	33.88±11.95	31.23±6.31		
CDSS				
T0	1.80±2.04	3.46±4.27	.94 (.39)	.17 (.68)
T1	3.68±3.73	1.77±2.52		
Speed of processing				
T0				
T1	24.48±9.99	27.69±9.23	2.32 (.11)	**6.28 (.02)***
	24.68±7.11	34.15±14.59		
Verbal learning				
T0	33.36±8.64	34.08±8.94	**12.39 (.00)***	**11.55 (.00)***
T1	31.84±6.01	47.62±9.86		
Working memory				
T0	29.24±10.76	31.38±9.94	1.05(.35)	1.87 (.18)
T1	29.64±11.16	35.62±11.13		
Reasoning and problem solving				
T0	32.28±4.71	34.00±9.46	1.94 (.15)	**9.84 (.00)***
T1	30.08±3.90	39.23±8.17		
Visual learning				
T0	35.92±14.06	36.92±17.34	1.51 (.23)	**5.20 (.03)***
T1	33.24±12.19	48.23±16.15		
Attention/vigilance				
T0	28.36±9.03	34.08±11.02	.19 (.83)	**4.64 (.04)***
T1	27.40±7.27	33.62±13.96		
Social cognition				
T0	27.40±10.74	28.62±6.33	1.40 (.25)	**6.72 (.01)***
T1	25.52±5.90	32.69±10.34		
SLOF phisical conditions				
T0				
T1	24.60±1.04	24.85±.38	.69 (.50)	2.47 (.12)
	24.40±.91	24.92±.28		
SLOF self-care				
T0	32.76±2.77	31.31±3.75	.29 (.75)	.32 (.57)
T1	32.27±2.49	32.46±2.22		
SLOF Int_Rel				
T0	22.12±4.29	20.62±6.07	.78 (.46)	.87 (.36)
T1	20.80±5.31	22.92±5.96		
SLOF Soc_Accet				
T0	34.54±.87	31.44±4.12	2.58 (.08)	**5.22 (.03)***
T1	34.77±.44	32.80±3.86		
SLOF Activities				
T0	47.76±5.67	44.31±6.74	1.48 (.23)	.12 (.73)
T1	44.48±6.96	44.31±5.14		
SLOF Work_skills				
T0	19.64±5.37	16.38±5.72	.54 (.59)	.045 (.83)
T1	20.34±4.89	19.92±5.60		
SLOF totale				
T0	179.12±17.35	175.00±18.70	.59(.55)	.14 (.71)
T1	175.84±16.77	178.62±11.76		

*Data are expressed as an average (standard deviation). Statistical analysis: ANOVA with repeated measures. * Significant value: p≤0.05. PANSS-P: Positive and Negative Syndrome Scale, positive symptomatology; PANSS-N: Positive and Negative Syndrome Scale, negative symptomatology; PANSS-G: Positive and Negative Syndrome Scale, general psychopathology; CDSS: Calgary Depression Scale for Schizophrenia; SLOF physical conditions: Specific Level of Functioning, physical abilities; SLOF Self-care: Specific Level of Functioning, self-care skills; SLOF Int_Rel: Specific Level of Functioning, interpersonal relationships: SLOF Soc_Accet: Specific Level of Functioning, social acceptability; SLOF Activities: Specific Level of Functioning, daily activities; SLOF Work-skills: Specific Level of Functioning, work skills; SLOF total: Specific Level of Functioning, general functioning.*

ing memory (a skill related to holding information in mind and manipulating that information), but accompanying evidence of a commensurate advantage in the reasoning/executive-function and problem solving domain in the CACR group is paradoxical as several studies have shown a close link between more elementary working-memory functions and higher-level reasoning and problem-solving skills [43]. Indeed, no effect was found in the domain of reasoning and problem solving when comparing computerized cognitive training to a control group in the meta-analysis of Prikken and colleagues (2019). This might be not surprising, as problem solving is a complex skill which is of great importance in everyday functioning [44]. Teaching strategies used by the therapist during and after CACR sessions in our study could explain our results. Indeed, the one-to-one interaction with a therapist who can explicitly encourage "bridging" strategies, as well as provide nonspecific support and motivational coaching form a meaningful components of the CACR therapy.

The same applies to social cognition: we found significant effect for this domain in the CACR group compared to the control active group. Social cognition is the set of mental functions that allow individuals of the same species to interact with each other, is defined as the ability to understand, predict and respond appropriately to the thoughts, feelings and behavior of others in social contexts different and often unfamiliar [45 46]. In literature, there are some studies that have tested the effects and possible improvements in social cognition, after CACR. Almost all agree that when coupled with rehabilitative programs focused on emotional intelligence, the benefits on recognition of emotions and the ability to interpret the feelings and behavior of others are more [47 48]. The three studies included in the meta-analysis of Prikken and colleagues did not detect a connection between CACR treatment and an improvement in emotional intelligence [11].

Moreover, the analysis regarding functional outcome resulted in a very small effect, as CACR was effective in improving only *SLOF Social Acceptability subscale*, in which are evaluated different aspects: the possible presence of verbal, physical abuse, physical aggression towards oneself, reiteration of certain behaviors (steps, oscillations, etc.), whether the subject destroys goods, whether the patient shows fear, cries or appropriates the property of others without authorization. A treatment period of a maximum length of 6 months may have been too short to rate more functioning differences between treatment groups, as some changes in the real-world functioning may take a relatively long time before becoming apparent, such as one year or more.

Conflicting results are reported in literature. Small to moderate, but only marginally significant effects on functional outcomes were found in the meta-analysis of Prikken et al. (2019), in contrast with other ones, that included also studies using strategy training, showing larger and significant effects [10 16 17].

This might suggest that CACR training alone might not be sufficient to improve daily functioning. Learning strategies might be a prerequisite for generalization of CACR treatment effects, as improvement of NC does not translate into improved social functioning [49 50]. It has been hypothesized that CR improves capacity to learn through increased verbal memory or executive functioning, and in the absence of concerted learning opportunities, improved cognitive functioning does not automatically lead to improved psychosocial functioning, as discussed in McGurk et al. [9 51]. Indeed, it was then demonstrated that CR is more likely to influence functioning when patients are given the opportunity to train cognitive skills in the context of a social learning environment through transferring skills from laboratory to real world and if it is combined with other psychosocial rehabilitation programs [16 50]. Our protocol study also focused on transferring learned abilities to the real world through 10-minutes discussion with the therapist at the end of each CACR session.

Moreover, the differences in literature could depend on the different scales administered to patients.

Finally, our results corroborate those of previous studies which showed a non-specific impact on symptoms in the CACR group [52-54] and are only partially consistent with evidence from Prikken et al. (2019), who showed a significant improvement of positive symptoms after CACR relative to a control condition, whereas small to moderate, but only marginally significant effects on negative symptoms were found. No effect of CACR on general symptoms was detected.

This study presents limitations and strengths. As for the formers, a first limitation of this study is its relatively small sample size: further studies on larger populations would be necessary to investigate more closely the relationship between type of treatment and cognitive functions, functioning in real life and symptomatology. Secondly, in this study only patients in stable phase of disease were included: it remains unclear to what degree these findings would generalize to patients earlier or later in the course of their illness, in long-term inpatient or nursing home care, or who are in comorbidity with substances abuse. Third, there was no independent randomization. But NC and symptoms were assessed blind to group allocation which strengthens our results. However, as our study was not blinded and patients receiving the intervention were offered increased attention, clinical care, and individualized contact on a frequent basis, this may have possibly influenced the positive cognitive outcomes in this group. Fourth, another factor that theoretically has the potential to influence whether CACR is found to be effective or not is choice of the control intervention. Although use of an active control may be desirable, it is important to ensure that the control task is sufficiently different from therapy to avoid it itself having positive beneficial effects on cognition [55]. The control active group we employed engaged cognitive functions, not of a drill and practice type. It makes at most minimal demands on executive function, and while it does require memory, this is procedural memory, which is universally considered to be dissociable from episodic memory as trained in CACR [56]. Also arguing against the possibility that our control intervention was therapeutic is the fact that we found significant differences at the end of the trial between the CACR and the active control group on some neuropsychological measures. Fifth, the fact that the study was conducted in an open unit, where patients had an opportunity to go out to the community might have

impacted the results, introducing uncontrolled variables, i.e., time spent in the community. Future studies could ensure that the active control task does not contain any form of cognitive training, although this could be extremely hard to accomplish. Sixth, the study could be viewed as lacking enough power to detect eventual differences between CACR and control group. This is a common problem in CACR trials, as detection of small effects requires large samples. Recruitment of large groups of patients is a great challenge, especially if it is conducted in a single unit. The duration of the study would substantially extend given that interventions take several weeks [57]. Lastly, we did not evaluate the long-lasting effects of these treatments after their discontinuation.

Some strengths of this study should be noted, including the well-matched baseline clinical, demographic, and cognitive characteristics of the two groups; the strict inclusion criteria; the absence of comorbid conditions that may have biased the study outcome measures; the accurate evaluation of cognitive functions, performed through the MCCB, and real-world functioning, evaluated through the *Specific Level of Functioning Scale* (SLOF), indicated as the best scale to estimate psychosocial functioning of schizophrenia patients among those included in the VALERO program. Lastly, diagnoses were based on structured clinical interviews and all patients were evaluated by trained raters.

In conclusion, if confirmed, our data suggest the importance of CACR aimed at implementing cognitive skills, social cognition and functioning in daily life in patients with schizophrenia.

Future studies are necessary to determine the durability of the improvements. While the effectiveness of the CACR has been demonstrated, further studies are needed to assess the effects over time.

Declaration of interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Substance screening in a sample of "clubbers": discrepancies between self-reporting and urinalysis

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Abstract

Substance use disorder (SUDs) and addicted behaviours are a serious social and economic issue, becoming increasingly common among the world's population and responsible for a considerable fraction of premature and avoidable deaths among young adults. In recent years, new issues of concern are represented by novel psychoactive substances (NPS) in addition to classic substances of abuse and their massive impact in specific realities, such as Ibiza, the most popular holiday destination for youngsters looking for entertainment; holidays in general and summertime in particular seem to represent a risky time of excess and experimentation, where illicit drugs are typically heavily promoted and widely available. Preliminary studies conducted in Ibiza nightlife resorts highlighted that, in both young tourists and foreign casual workers, risky behaviours appear to be considerably exacerbated, including alcohol and drug use, complex polyabuse and sexual risk taking. Evaluation of illicit drug consumption is supported by two assessment methods: self-reporting questionnaires, mostly used and practice and urinalysis, which is considered the gold standard for detecting the presence of substances but also for monitoring treatments, to support diagnosis and provide an epidemiological basis in studying patterns of drug abuse.

The current study aims at comparing data arising from self-reporting and urinalysis obtained by a sample of subjects admitted to a psychiatric unit after the intake of psychoactive substances for recreational purposes, and at evaluating factors associated with concordance or discordance between the two assessment methods, considering their limitations and strengths.

Introduction

Substance use disorders (SUDs) and addicted behaviours are a serious social and economic issue, with a major adverse impact on public health and welfare worldwide [1-3]. SUDs are becoming increasingly common among the world's population: the prevalence of illicit drug use in Europe and the number of drug-related deaths remain high; moreover, overdosing illicit drugs is responsible for a considerable fraction of premature and avoidable deaths among young adults, accounting for an estimated 4% of all fatalities among those aged 15–39 in Europe [4]. Frequently, fatalities are associated with injecting drugs and, in most cases, involve a combination of substances [4-6]. From 1990 to 2012, between 6100 and 8500 overdose victims were reported each year in Europe. Despite major increases in the provision of drug treatment in Europe, the overall number of reported overdose deaths increased between 2003 and 2008, although it has since fallen back to an estimated 6500 overdose deaths per year in 2012.

In recent years, new issues of concern are represented by novel psychoac-

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tive substances (NPS) in addition to classic substances of abuse [7-11]; there is currently a relevant body of clinical evidence to demonstrate the potential acute and chronic health harms associated with the use of NPS, but often very little is known by both consumers and health care professionals [12-15].

The scale of the phenomenon is impressive, but not known in full; for that, an in-depth assessment of substance-use and users is crucial for a global diagnosis and specific treatment plan.

Overall substance use is an undoubtedly global issue, but its impact is much more dramatic in some specific world areas than in any other place: the prime example may be the island of Ibiza, the most popular holiday destination for youngsters looking for entertainment; holidays in general and summertime in particular seem to represent a risky time of excess and experimentation [16]: illicit drugs are typically heavily promoted and widely available, thus, globally increasing revellers engagement in health-endangering behaviours during their stay [17]. Preliminary studies conducted in Ibiza highlighted that, in both young tourists and foreign casual workers, risky behaviours appear to be considerably exacerbated, including alcohol and drug use, complex polyabuse, and sexual risk taking [18-21].

In order to provide a quantitative assessment as accurate as possible with regards to substance consumption, urine testing represents the gold standard for detecting the presence of substances in the management of patients; urinalysis has been used not only for a simple evaluation of samples, but also for monitoring treatments, to support diagnosis and provide an epidemiological basis in studying patterns of drug abuse [22-24]. However, urine test should follow a primary assessment, using self-report measurement techniques [25]. Despite their crucial role in detecting the real impact of illegal drug abuse, both urinalysis and self-report techniques show limitations. Evaluation of illicit substance use based on the subjects self-report is the most widely used and practice [26] for epidemiological research in addictive behaviours because of its main characteristics such as low cost, flexibility, adaptability, efficiency, portability, the possibility to collect data through a variety of technologies (telephone, computer, video) and also the possibility of collecting an abundance of information from many people.

The current study aims at comparing data arising from self-reporting and urinalysis obtained by a sample of subjects admitted to a psychiatric unit after the intake of psychoactive substances for recreational purposes, and at evaluating factors associated with concordance or discordance between the two assessment methods.

Materials and methods

Study subjects and recruitment

48 subjects were enrolled between June 2015 and September 2015, as they were consecutively referred to the *Psychiatric Unit of Can Misses Hospital* (Ibiza, Spain). All the subjects who agreed to participate signed a written informed consent and were primarily evaluated by a team of psychiatrists using the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) criteria.

Inclusion criteria were: being aged between 18 and 75 years; intake of psychoactive substances or more than five alcohol units during the previous 24 hours. Exclusion criteria included: current presence of delirium tremens or hallucinosis at the moment of clinical interview (possible re-evaluation when clinical conditions improved); epilepsy; severe cardiac failure; diabetes mellitus; severe liver impairment; liver encephalopathy; kidney failure; neoplastic diseases; pre-existing dementia and other neurological diseases.

Variables and instruments

Sociodemographic characteristics such as age, gender, living status, job status, and level of education were investigated to outline a preliminary profile of the sample. Alcohol and substance use (tobacco, caffeine, cannabis, stimulants, depressors or NPS) were evaluated later through self-reporting techniques. In addition, all patients were assessed both at the admission (T0) and at discharge (T1) through several psychometric scales: PANSS (*Positive and Negative Symptoms Scale*), SCL-90 (*Symptom checklist 90*), YMRS (*Young Mania Rating Scale*), HAM-D (*Hamilton Depression Scale*), HAM-A (*Hamilton Anxiety Scale*), MOAS (*Overt Aggression Scale*), C-SSRS (*Columbia Suicide Severity Rating Scale*), in order to explore different psychopathological aspects or behavioural disorders.

Self-report

TLFB (*Timeline follow-back for psychoactive substances and alcohol*) was crucial to identify the main substances of abuse for each subject: a self-administered questionnaire was given to the sample, and included variables related to the use of alcohol and other drugs, aspects of personality, favourable attitudes toward use of cocaine and cannabis, for alcohol and ecstasy and also items which asked whether subjects had used these substances the weekend before admission.

Biochemical analysis

As a direct measure of recent use (previous 72 hours), a biochemical urine sample was collected from the patients at T0, stored at – 30°C, and subsequently analysed using HPLC technology, which represents a peculiarly versatile analytical platform.

Both for the TLFB and the urinalysis collection were carried out in an anonymous and confidential way. All participants received a detailed explanation of the design of the study, and written informed consent was systematically obtained from every subject, according to the Declaration of Helsinki. Ethics approval was granted by the *University of Hertfordshire Health and Human Sciences ECDA*, protocol no. aPHAEC1042(03); by the CEI Illes Balears, protocol no. IB 2561/15 PI; and by the *University G. d'Annunzio* of Chieti-Pescara, no. 7/09-04-2015. Data were securely stored and made accessible only to the research team members.

Results

The analysis of the data shows some interesting sociodemographic characteristics which could have a significant

impact on the following evaluations: males represent the vast majority of the sample, with a percentage of 67,3%, compared to females (32,7%); with regards to nationality of the subjects enrolled, Spanish is predominant (54,2%), followed by British (16,7%), Italian (6,3%) and others (Lebanon, Canada, France, Netherlands, Colombia, Germany, listed by frequency). Data concerning the level of education highlight an upper-intermediate grade: graduated, under-graduated and post-graduated represent the 56,3% of the population. The educational factor reflects the mean age of the tested population, which is around 33 years old: the majority of sample is represented by young and single (64,3%) workers or unemployed (51,1% and 46,7%, while a mere 2% were students) who often live with parents/partners (26,7%) or alone (17,8%).

Another crucial element in the global evaluation of the study sample concerns the presence of a positive previous psychiatric history: up to 80% of the subjects refers a known psychiatric diagnosis and/or an acute previous admission to psychiatric units.

In a preliminary analysis of self-reporting questionnaires, subjects who reported alcohol abuse were only 8,3%, compared to those who consider themselves non-abusers (91,7%); with regards to illicit substance use, a marked gap can be identified too: subjects who declare substance use were only 29,2%, while 70,8% did not admit illicit substance consumption (Fig. 1).

A more specific evaluation obtained by combining self-reported results and urinalysis showed that 3 males who referred alcohol consumption had no evidence in urine sample; likewise, only one female reported use of alcohol the weekend before but urinalysis of the patient were positive for desmetildiazepam and tramadol. Only one subject referred alcohol abuse in association with drugs (cannabis or cocaine) or binge-drinking disorder.

Regarding to substance abuse, this is a controversial issue since patients who declared substance use often presented a negative urinalysis or results did not meet the declared drug intake.

In detail, the most commonly declared substance was cannabis (5 subjects), alone or more often in association with cocaine (7 subjects).

Cocaine intake alone or associated with other psychoactives such as GHB, MDMA, speed, ketamine was less frequent (2 cases), while 13 patients admitted a polyabuse condition (three or more drug intaken simultaneously) based on the combined consumption of cannabis/cocaine/MDMA; cannabis/cocaine/heroin/BDZ; cannabis/NO/MDMA; cannabis/cocaine/LSD; cannabis/ketamine/cocaine/ecstasy/GHB.

Comparing urinalysis and self-reported declaration, concordant and discordant findings arose: 7 subjects admitting cannabis use (alone or in association with other drugs, mainly cocaine) showed positive urine testing for THCCOOH; similarly, 5 patients declaring cocaine use / alone or combined with cannabis/MDMA/heroin) presented BENZOILECGONINE in urine samples.

The concordance rate between self-reporting and urinalysis seems to decrease among polyabusers, because substances like ketamine, MDMA, GHB, heroin and ecstasy did not match in the urinalysis of the subjects enrolled; furthermore, 7 males who self-reported cannabis use alone or cannabis/cocaine association report positive urine for DESMETILDIAZEPAM and OXAZEPAM but no evidence of THCCOOH or BENZOILECGONINE.

Three subjects denied the use of psychotropics, drugs, or alcohol but their urinalysis showed DESMETILDIAZEPAM and CITALOPRAM positive results; on the contrary, 7 subjects that admited cannabis or cocaine occasional consumption presented negative urinalysis for drugs. Only one female who declared no illicit substance use report effectively negative urinalysis (Fig. 2).

Limitations

Several studies proved that the sensitivity of self-reporting could be increased when data are collected with clear instructions to respondents, combined with methods to im-

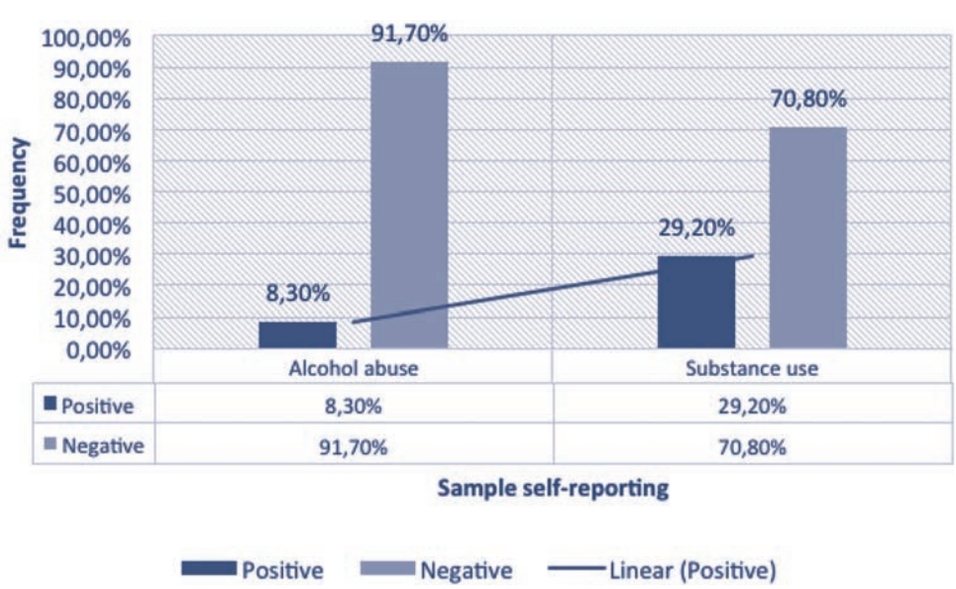

Figure 1.
Sample self-reporting.

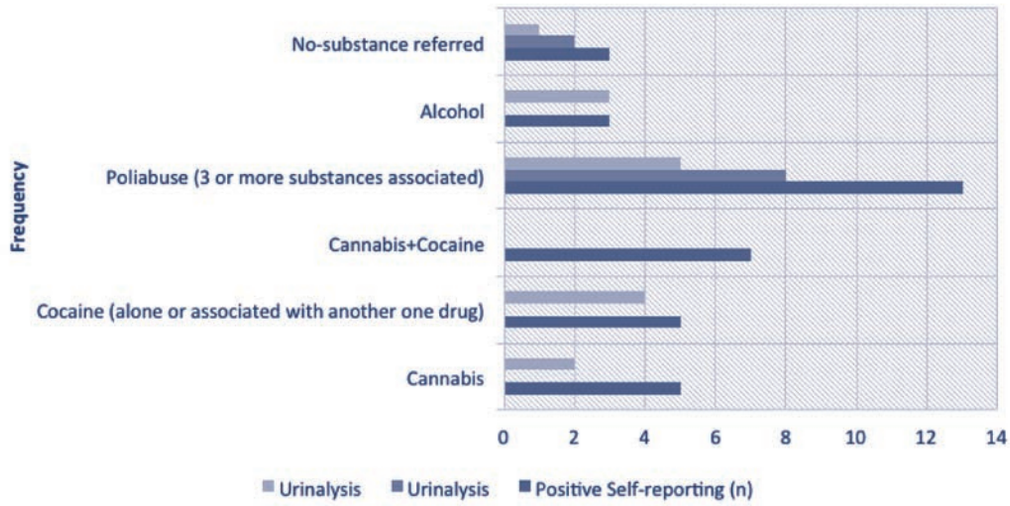

Figure 2.
Combined evaluation of self-reporting and urinalysis of the sample.

prove their motivation and to facilitate cognitive processing [26-28]. Nevertheless, the procedure presents several weak points: a well-known issue of self-reports is the uncertainty about their ability to accurately indicate what has really being measured. The validity of self-reported data is questionable, especially when the topic is sensitive or embarrassing: individuals may fear that disclosing illicit substance use could cause them legal problems or they may merely dread public opinion towards regrettable behaviours such as drug abuse. Therefore, even if confidentially is obviously guaranteed, fear of disapproval, punishment or embarrassment underpin the under-reporting phenomenon, which primarily affects the analytical reliability of self-reporting.
Although less common, the opposite phenomenon of over-reporting can also occur: subjects may over-report their consumption in order to get more medical prescriptions to avoid a withdrawal syndrome.
Evaluations based on gender revealed that males are more likely to under-report crack-cocaine use than females [29]; on the contrary, several studies focused on the validity of self-reporting across racial groups [30-32]. On the other hand, age differences in the validity of reporting abuse behaviours were initially noticed by Korotitsch & Nelson-Gray, R.O. (1999) [33], who showed that younger respondents provided more accurate self-reports than older ones, and later by [34] who found that younger respondents under-reported crack use but not marijuana use. Controlling for differences in base rates finally showed that drug offenders were more likely to under-report than non-drug offenders [35]. Despite certain differences in terms of gender, age, race or type of drug used have been highlighted, no statistical evidences regarding the basis of misreporting are still, to this day, revealed [36]. Even if self-reported data are usually cheaper to obtain, more practical and allow to gather more detailed information in comparison to biological markers, the above-mentioned issues related to risk of under- or over-reported drug use and limitations regarding psychosocial factors, unreliability of the subjects answers highlight that the self-report cannot be solely used for evaluation of substance use [37 38] and indicate the need for more effective and sensible diagnostic technique combining with this evaluation [39].
Currently, urinalysis is the favoured method for validating self-reported retrospective information to define drug use behaviours, becoming the gold standard to obtain a definitive diagnosis, to plan intervention, to monitor progress following treatment and also to provide an epidemiological instrument to provide patterns of drug abuse [22]. Unlike the self-reporting, urine screening is regarded as a more accurate measure of drug consumption because it is not subject to the potential biases related with the first one [40], but it also introduces limitations [41]: in addition to the higher cost of urine screen, its accuracy is crucially dependent on the sensitivity of the method, quantity of drug used or time since its use and the retention time of the substance [42-44].
Limitations in both survey methods form the basis of the evaluation regarding the level of concordance between self-reporting and urinalysis which are the aim of this study; several previous studies examined the causes of concordance or discordance among the two screening methods, underlying three types of factors: patient demographic characteristics, drug-use-related factors and treatment-related factors [30 42 45-47]. More recent studies showed that the level of concordance between self-report and urinalysis often reflected by kappa value which depends on many factors such as types of subjects, context of assessment and confidentiality of patient reports [47-49].
In conclusion, the need to combine self-reporting data and urinalysis in screening of drug abuse seems to be proven, but there is still doubt about the level of concordance between them [50].

Discussion

In light of published literature and above descripted results, a clear discordance between self-reporting and urine screening test emerges in the majority of the sample. Socio-demographical characteristics (sex, age, education and employment status) showed no significant evidence in determining discordance effects, even if in younger males who consumed cannabis [51] the concordance rate between the two methods is sensitively higher than among females and older patients. This may be mostly due to the different

kind of subjects evaluated, better fitting a 'clubber' profile and attending night-times social venues, more specifically night clubs [51-54]. Indeed, the recent growth of the clubbing phenomenon in the UK means that each week many young individuals, frequently using recreational drugs [55] such as NPS, attend late night dance venues, and each summer a relevant part of them seeks for holiday resorts abroad offering similar dance and social opportunities, increasing the dangers from consuming unexpected substances [56]. Clubbers are young, medium-high cultured and males in most cases, and they often consume illicit substances for recreational activities, to get used to the scene, or to ease sex [57 58]. This might explain why only a minority of the sample declares a habitual consumption of psychoactive substances [59], while in almost all cases is referred an occasional use of cannabis, alone or in association to GHB, MDMA, synthetic cannabinoids.

Moreover, discordance between reporting and biochemical analysis may depend on the detection window of urine testing, which is estimated around 72 hours for some drugs (cocaine and others), although cannabis can be detected until several weeks later in case of chronic use [60]. When no substance was identified, it was possible to hypothesise: (a) the presence of a psychoactive substance that could not be identified by common analytic methods; (b) the use of a substance with a short half-life; or (c) the consumption of a substance more than 72 hours before evaluation. The first scenario results particularly relevant in accordance with the extremely diverse characteristics of drugs, NPS in particular; indeed, one of the distinctive element of the NPS market is its ever-changing nature [61]. Compounds that are included into the narcotics legislation often decline/disappear from the market (with the exception of a few compounds) and new substances are introduced as their replacements. Therefore, the lack of knowledge about the whole composition of this substances could invalidate the conventional urine screening methods, often posing the question of revalidation; not least in terms of the chemical and metabolic structure, NPS cause quite a few diagnostic issues: from a chemical point of view, some NPS reflect simple modifications of controlled substances by changing the structure of known psychoactive substances or alternatively, substances with entirely different chemical structures are created. However, classic NPS subjected to legal control are immediately replaced by new uncontrolled derivatives and structural isomers of controlled substances frequently appear. Furthermore, analysing urine samples, possible metabolisation of the parent analytes should generally be considered and while synthetic cannabinoids show extensive metabolism to the point where most of the time only metabolites are detectable in urine samples, cathinones are metabolized to a far lesser degree; in the case of cathinones and piperazines, parent compounds are generally abundant in urine, for piperazines even in higher concentrations than their respective metabolites [62].

Another issue that should be taken into account is the fact that some of the parent compounds may be metabolites of other substances such as ephedrine and norephedrine can be formed by either metabolic reduction of methcathinone and cathinone, respectively, or oxidative metabolisation of methamphetamine and amphetamine, respectively. Taken into account these considerations, the high level of discrepancies still need to be explained. Several factors could contribute to this gap: the fear of social judgement often seems to be related with an under-report of substances morally stigmatised like heroin, LSD, MDMA, GHB or alcohol while widely-consumed drugs (cannabis at first and cocaine, too) are self-reported often associated with a positive urinalisys for THCCOOH (related with cannabis) or BENZOILECGONINE (cocaine urinary metabolite). Another arising element is the underestimation of BDZ as illicit substances: patients under-reported or totally denied BDZ consumption, but related urinalysis result positive for DESMETILDIAZEPAN or OXAZEPAM in the same subjects; the reasons behind this type of discordance could depend on the lack of knowledge about this substance itself: BDZ are often consumed in association with cannabis, probably to obtain a relaxing effect and it is not seen as a drug per se, but as a medication (or medicine).

However, patients are not always liars. Indeed, in some cases they are not aware of substances that they are consuming, but they totally trust the dealers and refer what they think they are consuming. Here the controversial subject of counterfeiting substances comes into play: in order to reduce the costs of street drugs production and to attract an even increasing population, the drug marketing developed metabolites structurally similar to the most common substances of abuse, but even more harmful and hard to identify through the main screening tests. This is the case for illicit fentanyl (fentanyl-contaminated heroin or FCH), for whom the lower price and potency make it frequently used as adulterant in street heroin, cocaine, and methamphetamine, or as heroin substitutes sold to unaware users with a high risk of overdoses. Fentanyl and its analogues have also been identified in counterfeit medicinal products, such as oxycodone, hydrocodone, and alprazolam tablets, or as components of speedball mixtures together with cocaine or other stimulants [63-65]. NPS also fit that description since they can be brought quickly to market, and since they are technically not illegal, they are often promoted as 'legal highs'. Many NPS products arrive at specialty shops and can be sold with little to no legal restraints in communities where authorities may be oblivious to their availability (*United Nations Office on Drugs and Crime*). A further example of counterfeit drug produced to stretch product cheaply is Fenethylline [66], also known as amphetaminoethyltheophylline and amfetyline, a combination of amphetamine and theophylline, which behaves as a prodrug to both of the aforementioned drugs. It is also marketed as psychostimulant under the brand names Captagon, Biocapton, and Fitton [67]. Consequently, all this evolving drug market represents a great and grave defect to the sample evaluation, mainly highlighted in the urine screening test: none of the subjects tested reported use of combinated drugs (that they are not aware) and they are not revealed in urinalysis.

In other cases, substances self-reported are not reflected in urinalysis results, which appear negative: this may due to subjects, who are not accurate in describing time and frequence taking or to misdelivery and processing mistakes of urine sample [36 68].

In conclusion, according to the findings mentioned above, it is clear that there is no certainty regarding all discordance causes between self-reporting and urinalysis but further research that target the optimization of assessment procedures combined with a more careful simultaneous evaluation of them could well allow a decrease in the discrepancy-phenomenon.

Conflict of interests

The authors declare no conflict of interest.

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Commentary on the current Guidelines in Psychopharmacotherapy

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Introduction

Psychiatry is frequently perceived as a 'soft' science and treatment of mental illness can be mis-perceived as not focused nor specific, thus allegedly not effective.

In the last decades, the need to standardize different therapeutic approaches and to reduce incorrect practices has encouraged the development of guidelines to advise on the treatment, management and assessment of psychiatric disorder [1].

Publication of evidence-based practice guidelines supports the recognition of the scientific approaches of psychiatric treatment and improves health care delivery by decreasing inappropriate variation in clinical interventions [2].

Implementation of these guidelines accelerates both the acquisition and the dissemination of new scientific in-depth knowledge, as clinicians and researchers are better able to identify similar illnesses and compare findings. At the same time, compliance to practice guidelines can increase the comparability of treatment approaches and stimulate more effective research [3].

While playing an important role to assist clinicians in their decision-making, treatment guidelines suffer for a number of limitations. Some psychiatrists claim that the use of guidelines would contribute to a culture of "cook-book medicine"; others are concerned about the lack of implementation strategies and the risks of potential escalation of malpractice litigations.

Moreover, there is also an objective gap in research base (especially for long-term treatments and patients with comorbid conditions) that creates further complexity when providing recommendation under clinical consensus [4].

Clinical guidelines can be defined as "systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific clinical circumstances" [5].

Internationally they have been developed by professional associations, by government agencies, by insurance companies and other third party payers, and by providers of care.

In scientific literature, guidelines that meet the 5 following specific criteria are identified as "good" guidelines. In detail, it occurs when the guidelines:

- are developed by physicians in active clinical practice;
- integrate relevant research and clinical expertise;
- describe specific treatment approaches, including indicators, efficacy, safety and alternative treatment strategies;
- are reviewed and revised at regular intervals not longer than 5 years;
- after approval, are widely disseminated.

Notwithstanding recent developments, there are difficulties in clinical application. Only a few studies analyze the applicability and the implementation of treatment guidelines in psychiatry.

The guidelines, according to the latest medical culture, provide recommendations based on scientific evidence and standards of good clinical practice useful for guiding and supporting the decisions of all professionals working in the various medical specialties, including psychiatry.

However, it is necessary to keep in mind that the guidelines are not rigid and rigorous protocols to be applied indiscriminately but it is necessary to take

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into account the clinical characteristics of the individual patient, as well as his expectations regarding treatments and preferences motivated also by ethical aspects.
Another important aspect is that most of the real-world patients are characterized by multi-morbidity and the balance between risk and benefit of planned care is often unpredictable due to the fact that efficacy tests derive from studies carried out on selected patient groups that often they do not take into consideration patients suffering from multiple pathologies.
Despite this premise, one cannot deny the great positive impact that the development of guidelines based on scientific evidence has made for medicine.
It is not possible to establish a ranking of importance or completeness with respect to the various guidelines present in psychiatry to date. Some of the most well known and widely accepted guidelines, taken into account by psychiatrists in daily clinical practice are listed in Table I.
Specifically, the CANMAT previously published treatment guidelines for bipolar disorder in 2005, along with international commentaries and subsequent updates in 2007, 2009, and 2013. The last two updates were published in collaboration with the *International Society for Bipolar Disorders* (ISBD). The main objective of these publications was to synthesize the wealth of evidence on the efficacy, safety, and tolerability of the range of interventions available for this complex and varied illness, with the goal of providing clear, easy to use recommendations for clinicians to improve outcomes in their patients. The 2018 CANMAT and ISBD Bipolar Treatment Guidelines represent the significant advances in the field since the last full edition was published in 2005, including updates to diagnosis and management as well as new research into pharmacological and psychological treatments.
These advances have been translated into clear and easy to use recommendations for first, second, and third line treatments, with consideration given to levels of evidence for efficacy, clinical support based on experience, and consensus ratings of safety, tolerability, and treatment-emergent switch risk.
A hierarchical rankings were created for first and second-line treatments recommended for acute mania, acute depression, and maintenance treatment in bipolar I disorder. This hierarchy will further assist clinicians in making evidence-based treatment decisions.
In addition to addressing issues in bipolar I disorder, these guidelines also provide an overview of, and recommendations for, clinical management of bipolar II disorder, as well as advice on specific populations, such as women at various stages of the reproductive cycle, children and adolescents, and older adults. There are also discussions on the impact of specific psychiatric and medical comorbidities such as substance use, anxiety, and metabolic disorders. Finally, an overview of issues related to safety and monitoring is provided.
Psychiatry is a discipline that deals with the dimensions of human suffering and positions itself between psychology, sociology and biology. The psychiatrist therefore needs to have robust guidelines available that can support clinical decisions in the real world.
As a good practice, all the guidelines mentioned above should be uniform and precise. However, it seems that there are many differences when all the guidelines are compared.
According to the Guideline International Network [11], founded in 2002, high quality guidelines are defined in compliance with fundamental requirements and involve various phases, each of which can be managed with different degrees of methodological rigor:
• composition of the development group of the guideline

Table I. The most common international guidelines in psychiatry.

APA Guidelines *American Psychiatry Association* [6]	USA	Probably the most famous guidelines in Psychiatry as they also come from the association that deals with the management of the DSM-V diagnostic manual
NICE Guidelines *National Institute of Health and Care Excellence* [7]	UK	It has acquired a certain international authority, also as a model for the development of clinical guidelines not only psychiatric, based on evidence, literature analysis and cost/effectiveness evaluation. The NICE publishes guidelines in four areas of health: health technology (drugs and therapeutic procedures), clinical practice (appropriateness of the treatment of people with specific pathologies), prevention of diseases and occupational medicine
RANZCP Guidelines *The Royal Australian and New Zealand College of Psychiatrists* [8]	Australia	It is a mine of information not only on the most up-to-date and clear guidelines of psychiatry but also on many other current topics related to psychiatry (legislation, ethics, neuro-science, innovative and alternative treatments etc.). RANZCP addresses all diseases of both adult and adolescent patients and childhood
Maudsley Guidelines [9]	UK	The 10th edition of the *Maudsley Prescribing Guidelines* fully updates the 9th edition and includes new sections offering guidance on, for example, the use of psychotropic drugs in atrial fibrillation, alternative routes for antidepressant administration and the covert administration of medicines
CANMAT Guidelines *Canadian treatment guidelines and Canadian Network for Mood and Anxiety Disorders* [10]	CANADA	It focuses on mood and anxiety disorders, provides up-to-date scientific information, treatment guidelines and educational opportunities for physicians, as well as clear and helpful information on symptoms and treatments for patients and their families. CANMAT conducts research on the clinical management of diseases, pharmacological and psychotherapeutic treatments and biomarkers of mood disorders

that should include several relevant stakeholders (professionals, health professionals, methodologists, subject matter experts and patients);
- decision-making process used to reach consensus among the members of the group and, if applicable, for approval by sponsors. This process should be defined before starting the development of the guidelines;
- conflicts of interest of any type to be disclosed and potentially addressed;
- scope and objectives of the guideline to be clarified;
- methods to be stated;
- review of scientific evidence evaluated and identified with systematic methods;
- guideline recommendations to be formulated clearly and based on evidence relating to benefits, risks and, if possible, costs;
- rating of evidences and recommendations: to classify and communicate both the quality and reliability of evidence, to assess the strength of clinical recommendations;
- peer review and stakeholder consultation;
- validity and updating of the guidelines;
- financing and sponsorship.

Results

Translating scientific evidence into daily practice is complex. First of all there is inconsistent use of terminology, which contributes to difficulties in replicating and understanding the association between intervention and outcomes [12]. It was noted that while in some areas, the recommendations provided by the guidelines appear to be fairly uniform (eg Valproate in the case of acute management of mixed episodes, use of antidepressants and duration of long-term antipsychotic treatment), in other areas, they differed widely (recommendations on psychosocial management and duration of acute treatment of the mood episode).

The primary aim of clinical guidelines is to provide the best practice treatment, i.e. to increase the quality of care available to patients [4].

From patients and families perspectives, accepted guidelines can be considered an information tool that opens to a higher level of disclosure. Once informed about recommended best practices about treatment alternatives, under some circumstances, they have the chance to participate in implementation decisions as well.

The treatment of mental illnesses has grown very rapidly and in order to accept guidelines as reliable, clinicians need to review the extent and the nature of evidences related to the various interventions in the cure of the specific psychiatric disorders. Consequently, guidelines effectiveness ranks in accordance to the level of clinical confidence in the recommendation (weights of relevance) and the nature of supporting evidence (code of reference).

Guidelines also represent a relevant educational instrument; by leveraging on their comprehensive nature and the extensive, coded reference sections, they support clinical reasoning, literature search and provide data and analysis with easy and quick availability.

Although guidelines may be intended as a chance to bridge the gap between clinical research and evidence-based practice, they are not universally welcome. Many attitudinal and behavioral barriers prevent physicians from adopting them.

First of all, it is clear that comprehensive and relatively lengthy guidelines are not easily used in busy practices. It is often also a matter of attitude because there is no tradition in psychiatry of following clinical guidelines and, as a new approach, it requires great adaptation that sometimes is agreed upon after discussion of different psychiatric schools of thought and theories. Traditional treatment approaches can be questioned in the light of presented evidence and this can be addressed as a barrier [13].

Perception of appropriate guidelines and implementation strategies are also crucially important in order to build up the accepted consensus on reliable updated recommendations as well as to avoid oversimplification of complex clinical questions. In this latter case, known as the “reductionist approach to medical care”, clinicians refuse to practice “cook-book” medication to preserve their judgmental autonomy against excessive standardisation and trivialization of care [2].

Another limitation that can affect the guidelines development is the gap in research base because of the undeniable complexity of psychiatric disorders: a majority of patients who suffer from mental illness present comorbid conditions and experience them in the long-term. These factors take time for properly addressing the state of knowledge and the adequate tools for the evaluation of the care.

Moreover, it has been seen that the identified barriers to, and facilitators of, the implementation of guidelines could be classified into three major categories: (a) organizational resources; (b) health care professionals’ individual characteristics; and (c) perception of guidelines and implementation strategies [2].

In detail, the first category related to organizational resources involves:
- in terms of barriers, the risks of experiencing a lack of trust in the guidelines’ recommendations and an environment not supportive to clinical guidelines due to several reasons (e.g. no agreement on need to use clinical guidelines, lack of time influence of prior experiences, lack of organizational strategy and skills, resistance to multi-disciplinary team, etc.). Furthermore, financial concerns on cost control and standardization of care might threaten the doctor or therapeutic-patient relationship;
- in terms of facilitators, multi-disciplinary implementation team with clear roles, awareness of clinic attitudes and actions, feedback on performance and quality indicators.

With reference to health care professionals’ individual characteristics, as mentioned above, personal behaviours and attitudes can significantly affect the approach to guidelines in favour or in opposition to them. Positive beliefs regarding evidence-based treatments and new actions, and high levels of practitioner’s awareness support the definition and implementation processes of guidelines, while the lack of knowledge, skills and motivation, the fear of loss of autonomy and of standardised care, together with insufficient dedicated time and specialised training create a hostile environment for their development.

Promotion of learning culture, definition of precise roles,

awareness of clinic actions and effective team working in applying recommendations uphold positive perception of guidelines and implementation strategies, as well as easy access to tools and clinical scales.
On the contrary, the lack of familiarity and overwhelming amount of medical research, doubtful credibility of the recommendations and uncertain reliability of the sources are perceived as barriers to these strategies [1]. "Missing" recommendations, a lack of addressing issues believed to be important for clinical practice and for patients or a failure to internalize guidelines into clinical routines are also hurdles that influence the providers' willingness to accept guidelines [14].
The psychiatrist should base his work on solid scientific and clinical grounds. Diagnosis and therapy suggested by manuals and treaties of psychiatry with national and international diffusion, attention to the guidelines and protocols recognized by scientific societies are factual data justifying good clinical practice.
However, the principles of good clinical practice must be contextualised in that specific psychiatrist, with those specific clinical experiences and training, with that particular patient, in that specific psychopathological and psychosocial context in which the fact occurred.
This need, however, must not underestimate the limits of the guidelines and must lead the specialist to a critical acceptance of them in everyday clinical practice.
The guidelines are constructed with a methodology that takes little account of the opinions of experts in daily practice; they are linked to specific schools of thought that are not always shared; refer to ideally selected patients in ideal care settings for hotel, social and pharmacological assistance; they do not take into account the complex patients present in daily practice; they can be influenced by economic-managerial-insurance order priorities; they are different in the indications between them; often they change their principles over time; they can be used for a defensive psychiatry that does not privilege the patient's benefit [15].

Discussion

Standard clinical practice is usually guided by clinical guidelines. A good guide should be able to identify the Diagnosis, the evaluation strategy and the choice of the treatment, allowing to evaluate the benefits, risks and costs of the alternative decisions and presenting concise and updated recommendations. The guidelines should be able to guarantee the best clinical standards for doctors. However, they are often not read or followed because of poor quality or obstacles due to lack of agreement or ambiguity.
It was also noted that most of the guidelines provide more detailed recommendations in the field of pharmacotherapy, while dealing in general with psychosocial management.
An ideal guideline should derive from a complete literature review and should explicitly evaluate the quality of support research studies and the methods used to summarize the evidence. This guideline should provide recommendations for the management of pharmacological treatment, but also for evaluation and psychosocial interventions during the acute and maintenance stages of the disease [16].
There is therefore a need for internationally acceptable and culturally fair recommendations to be developed and then set the framework for further development on a national or local basis. International organizations such as the WPA or WHO may help formulate a unified guideline, which may then be modified to meet national or local needs.

Conflict of interests

The authors declare that there is no conflict of interests.

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Towards Italian guidelines for the pharmacological treatment of Obsessive-Compulsive Disorder (OCD) in adults: a preliminary draft

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Introduction

Obsessive-compulsive disorder (OCD) is a heterogeneous psychiatric disorder with a lifetime prevalence in the general population of approximately 2-3% [1]. It is currently classified by the DSM-5 within the chapter of "Obsessive-Compulsive and Related Disorders" (OCRDs), where it is the "*nosological organizer*", together with Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling Disorder) and Excoration (Skin-Picking) Disorder. ICD-11 will follow the DSM-5 and create an analogue chapter adding Olfactory Reference Disorder and Hypocondriasis (Health Anxiety Disorder) to the other OCRDs [2].
The diagnosis of OCD is made by the presence of recurrent or persistent, upsetting thoughts, images, or urges, that are experienced, at some time during the illness, as intrusive and unwanted (obsessions), and that cause anxiety or distress (at least in most individuals, although with time subjects may respond with compulsions before experiencing anxiety); the individual attempts to ignore or suppress the obsessions or to neutralize them by performing a compulsion. Compulsions, which follow obsessions in the vast majority of patients [3], are repetitive behaviors or mental acts performed in response to obsessions. By definition, compulsions are finalized behaviors (aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situations), unlike other repetitive acts like tics which are purposeless. Moreover, compulsions are intentional [4]. Together with obsessions and compulsions, avoidance behaviors are usually present, and such signs and symptoms interfere with individual functioning and consume time (at least one hour per day for the diagnosis).
Family members are also usually involved in symptoms, as they often directly participate in compulsions and in avoidance behaviors. The term family accommodation has been proposed to refer to family responses specifically related to obsessive-compulsive symptoms: it encompasses behaviours, such as directly participating to compulsions and/or assisting a relative with OCD when he/she is performing a ritual (e.g. controlling that the patient with OCD is "*correctly*" taking a shower without touching nothing "*dirty*" or potentially "*contaminating*"; having to pass towels to the patient taking particular care that they do not touch "*contaminated*" surfaces) or helping him/her avoiding triggers that may precipitate obsessions and compulsions (the relative has to respect rules that OCD imposes on the patient; e.g. for a patient with contamination obsessions, having to undress before entering home and putting the "*dirty*" clothes in a specific place at home, avoiding to "*contaminate*" the house with "*dirty clothes*" and having to immediately wash themselves before entering "*uncontaminated*" rooms) [5].
OCD has generally an early age at onset, in childhood or early adult life [6], with an earlier age at onset in males; the early age at onset may greatly impact on

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the ability of patients with OCD to gain normal skills and abilities to function in adult life [7]. OCD tends to have, in the majority of cases (up to 75% of patients), a chronic course; the picture is further complicated by the long duration of untreated illness, usually of 10 years or even longer [8,9]. OCD tends to run in families, because of a shared genetic predisposition combined with shared obsessive beliefs as cognitive vulnerability factors [10,11]. Cases of early onset, particularly in male patients, can show a high degree of comorbidity with tic disorders and attention deficit hyperactivity disorder (ADHD) [12].

Despite the availability of effective treatments for Obsessive-Compulsive Disorder (OCD), namely Cognitive-Behavioural Therapy (CBT) and serotonergic compounds (SSRIs and clomipramine) [13,14], there is a treatment gap (difference between those individuals with OCD needing treatment and those actually receiving it), estimated to be in Europe of 25% in 2004 (50% approximately in the world)[15]. The situation has not changed in more recent years: the proportion of subjects not being treated worldwide in more recent epidemiological studies, in fact, is estimated to vary between 22 and 92%, with 38-to-90% of individuals not even seeking treatment or advice for their OCD [16]. The phenomenon is then relevant. Even when subjects with OCD do seek help, the mean delay in help-seeking behaviours is substantial: it is estimated that individuals with OCD take up to 11 years to seek professional help [9,16,17]. Moreover, the interval between help seeking and receiving an *adequate treatment* for OCD is also significant (approximately 2 years for pharmacological treatment [18-20]). This means that a significant challenge exists for physicians and/or mental health professionals in recognizing and diagnosing OCD appropriately, or in prescribing or offering an *adequate* treatment (it may be that psychological therapies other than CBT with exposure and response prevention are applied, or that antidepressants other than clomipramine or SSRIs are prescribed, or for less than the required 12 weeks, or at sub-therapeutic doses). There is thus a strong need for early recognition, appropriate diagnosis and administration of adequate treatments for patients with OCD [20].

As a consequence, the duration of untreated illness (DUI), defined, in most investigations, as the interval between the onset of a specific psychiatric disorder and the administration of the first pharmacological treatment at standard dosages and for an adequate period of time, in adherent subjects, is remarkable in OCD patients. Indeed, DUI in OCD has been consistently demonstrated to count among the longest for any psychiatric disorder – in recent years ranging between seven and ten years in adults [17,19,21,22,23]. In addition, Italian studies found that the longer the DUI (≥ 2 years), the lower is the response to pharmacological treatments [9,19], suggesting a possible *damaging* effect of untreated symptoms even in OCD, as seen for psychotic disorders.

There is then a strong need for evidence-based, country-specific treatment guidelines that can help Italian clinicians to correctly prescribe and monitor treatments for individuals with OCD.

The aim of the present paper is to provide an overview of the state-of-the-art treatment of OCD, with a focus on the pharmacological treatment, and a preliminary draft for the development of Italian guidelines for the treatment of patients with OCD.

Evidence-based first-line treatments

First-line treatments for OCD include 1) pharmacotherapy with selective serotonin reuptake inhibitors - SSRIs – and, among the tricyclic antidepressants, only the serotonin reuptake inhibitor –SRI – clomipramine, and 2) cognitive behavior therapy (CBT) – in the forms of exposure and response prevention (ERP) and/or cognitive restructuring [24-33]. Both the above-mentioned pharmacological and psychological approaches have been recognized more effective than wait-list, inactive psychological treatments or placebo in double-blind randomized controlled trials (RCTs) and meta-analyses.

Pharmacotherapy, CBT or both? How to choose the personalized first-line treatment

Since both approaches are valid first-line treatments, a logical question is which approach is indicated for which patient and whether the combination *ab initio* of pharmacotherapy and CBT is more effective in reducing symptoms as compared to either monotherapy (medications only or CBT only). A recent systematic review [34] identified ten controlled studies assessing the efficacy of combination treatments ab initio *versus* CBT alone and six evaluating combination strategies ab initio *versus* medications alone. The combination *ab initio* of CBT and SRIs was not been found to be clearly superior to either monotherapy alone in most studies conducted in the field, except for patients with severe depression who might benefit more from the combination *versus* CBT only and children/adolescents.

OCD patients with comorbid major depression should then receive medication firstly, eventually associated with CBT; for all remaining patients, there is clear evidence from the literature of no additive benefits of combining *ab initio* CBT and medication. Therefore, the routine use of a combination approach in all adult patients affected by OCD is not supported by the literature.

These findings are consistent with the results of a recent network meta-analysis conducted by Skapinakis and colleagues [13], which stated that there is no sufficient evidence to suggest that combined treatment is better than psychotherapy alone, although combination of medication and CBT seems to be an acceptable treatment, mostly in severe OCD.

Psychological interventions are indicated by some guidelines (NICE guidelines) [33] as first-line treatment for the management of mild to moderate OCD, while for moderate to severe OCD, particularly when other psychiatric disorders are present (not only major depression), pharmacological treatment is indicated as a priority.

Pharmacological treatment: which drugs?

All SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and only clomipramine,

among the tricyclic antidepressants, are considered first-line drugs for adults with OCD. Venlafaxine proved to be as effective as paroxetine or clomipramine in double-blind or single-blind studies in adult patients with OCD; however, the lack of a placebo-controlled study demonstrating its superiority over placebo makes this compound a second choice in the pharmacological treatment of adults with OCD.

Although some meta-analyses indicate that the efficacy of clomipramine is greater as compared to that of SSRIs as a class in terms of standardized mean difference, effect size or NNT (e.g. Hirschtritt et al. [14]), individual head-to-head comparisons between different SRIs did not find statistically significant differences in efficacy. The choice between SSRIs or clomipramine is then conditioned by the higher burden associated with clomipramine in terms of side effects. SSRIs should be then prescribed as first-choice in adults with OCD. Clomipramine may be considered when there is poor response to an SSRI, a previous good response to clomipramine, or patient's preference.

Which dose?

Fixed-dose studies have been performed for all SRIs except fluvoxamine and clomipramine. The minimal effective dose for fluoxetine and paroxetine (the one that differed statistically from placebo in terms of response) is 40 mg/day, and for escitalopram 20 mg/day; for citalopram and sertraline there is an indication of greater efficacy at higher doses (40-60 for citalopram and 200 for sertraline). A meta-analysis [35] of all placebo-controlled studies in adults with OCD clearly confirmed that medium-to-high doses should be used for the pharmacological treatment of OCD in order to obtain the greatest efficacy. Table I provides minimum target and maximum doses to be used in OCD.

How to evaluate response and when

A recent international expert consensus [36] defined response as a ≥ 35% reduction in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score with respect to beginning of treatment (partial response ≥ 25% but < 35% reduction) (Table II); response in OCD is gradual, incremental and requires up to 12 weeks to be evident (usually it takes a minimum of 6-to-8 weeks for *initial* response to be evident). This is a huge difference with respect to response in major depressive disorder, where response is greater in terms of symptoms reduction (>50% on the HAM-D or MADRS usually) and occurs earlier (before weeks 4-8 generally). This difference has to be kept in mind, as it may happen that clinicians not fully aware of this slow response in OCD may be willing to change treatment after only 4 weeks, preventing the drug to be fully effective (the consequence is that patients are mislabeled as resistant).

When response, defined as above, is evident, continuation treatment, at the same dose, is associated with continued improvement in symptoms until remission is achieved [14].

Adherence should be monitored, especially in the first weeks of treatment, when side effects associated with pharmacological treatments may emerge while response is still lacking.

How long should a responder be kept on continuation/maintenance treatment?

Following adequate response, treatment should be kept with the same compound and with the same dose until remission is achieved [37]. Then, treatment should be continued for a further 12 months to prevent the risk of relapses [38-40]. Placebo-controlled, relapse prevention studies lasted up to 12 months, and not all SRIs underwent such trials. Several long-term, naturalistic studies showed that in some cases treatment can be safely continued for several years with maintenance of efficacy and prevention of relapses [41-45]. Severity of illness at baseline, prior duration of untreated illness (which may impact on response rates), number of previous episodes and persistent psychosocial adversities may suggest maintenance of treatment for 2 years or longer [19,20]. Of course, the persistence of residual symptoms as well as a partial response should suggest maintenance treatment and a further assessment of next-step strategies.

Although there is some evidence [41,46] that long-term main-

Table I. Doses of serotonin reuptake inhibitors (SRIs) in the treatment of OCD.

Drug	Starting dose and incremental dose (mg/day)	Usual target dose (mg/day)	Maximum recommended dose in Italy (mg/day)
Citalopram*	20	40-60	40[#]
Clomipramine	25	100-250	250
Escitalopram	10	20	20[§]
Fluoxetine	20	40-60	60
Fluvoxamine	50	200	300
Paroxetine	20	40-60	60
Sertraline	50	200	200

** Citalopram in Italy is not indicated for the treatment of OCD, although its efficacy is established in placebo-controlled, double-blind studies. [#] Citalopram is associated with dose-dependent QTc prolongation, thus in Italy the maximum dose recommended for adults is 40 mg/day (20 mg in patients > 65 years-old or with reduced liver function). [§] Escitalopram is associated with dose-dependent QTc prolongation, thus in Italy the maximum dose recommended for adults is 20 mg/day (10 mg in patients > 65 years-old or with reduced liver function).*

Table II. Definitions of response-remission (Mataix-Cols et al., 2016, modified).

	Conceptual	Operational
Treatment Response	A clinically meaningful reduction in symptoms relative to baseline severity	A ≥35% reduction in YBOCS scores plus CGI-I rating of 1 ("very much improved") or 2 ("much improved"), lasting for at least one week
Partial Response	Defined as in treatment response above	A ≥25% but <35% reduction in YBOCS scores plus CGI-I rating of at least 3 ("minimally improved"), lasting for at least one week
Remission	The patient no longer meets syndromal criteria for the disorder and has no more than minimal symptoms. Residual obsessions, compulsions and avoidance may be present, but are not time consuming and do not interfere with the person's everyday life	A score of ≤12 on the YBOCS plus CGI-S rating of 1 ("normal, not at all ill") or 2 ("borderline mentally ill"), lasting for at least one week
Recovery	The patient no longer meets syndromal criteria for the disorder and has had no more than minimal symptoms. The clinician may begin to consider discontinuation of treatment or, if the treatment continues, the aim is to prevent relapse	As above, lasting 1 year

tenance therapy for OCD may be provided with lower dosages of the anti-obsessional drug (50-to-66% lower than those used to achieve remission), with clear advantages for tolerability and compliance, all published International guidelines suggest keeping the same medium-to-high dose throughout the maintenance phase in order to prevent relapses.

Adherence to treatment is particularly important and should be monitored throughout the whole maintenance phase of the treatment, when remission is achieved (the patient no more suffers from symptoms) and patients may be more prone to forget to take medications as required. Preliminary evidence [39] suggests that relapses due to premature treatment discontinuation or to intermittent adherence respond less well when the same drug at the same dose is reinstated, indicating a possible "toxic" effect of relapses.

No clear indications emerge from the literature concerning how to stop medications after the maintenance phase in patients fully remitted: a slow titration regimen is preferable in order to prevent discontinuation symptoms associated with SSRIs (particularly common with drugs with short half-life).

Resistant patients

Treatment-resistant OCD patients are defined as those who undergo adequate trials of first-line therapies without achieving a satisfactory response, usually defined by a reduction in the Y-BOCS total score ≥35% or ≥25% with respect to baseline (see above for the definition of response and partial response) [47].

Practically, before confirming a condition of treatment-resistance, clinicians should follow these steps:

Check the appropriateness of the diagnosis of OCD; particularly, other symptoms should not inappropriately be considered as obsessions or compulsions (obsessive-compulsive personality disorder; ruminations occurring in Major Depressive Disorder or other Anxiety Disorders – e.g. GAD; repetitive stereotyped behaviours encountered in psychoses, in mental retardation, or in organic mental disorders; obsessive concerns about body shape or ritualized eating behaviours in Eating Disorders; patterns of behaviours, interests or restricted and repetitive activities in Autism).

Check that the patient has been exposed to an adequate pharmacological trial (SRIs) in terms of appropriate doses and for at least 12 weeks (see paragraphs above).

Consider potential medical or psychiatric comorbidities that could affect treatment response (e.g., paradigmatic the case of OCD comorbid with Bipolar Disorder, where treatment with high doses of SRIs could worsen both bipolar disorder – mixed episodes, rapid cycling, switch – and OCD).

Consider the possible negative role of family members or caregivers, who might be accommodating OC symptoms, thus counteracting the goal of the treatment and contributing to the maintenance of the disorder. 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.

Evidence-based (at least one positive randomized controlled trial versus placebo) treatment strategies for individuals not responding to a first trial with SRIs are:

- antipsychotic add on to SRIs;
- CBT add on to medications;
- switch to intravenous route of administration (if first-line treatment is clomipramine or citalopram);
- switch to paroxetine or venlafaxine;
- addition of medications other than antipsychotics to SRIs;
- use of brain stimulation techniques.

a. Antipsychotic addition to SRIs

The use of antipsychotic add on 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

Table III. Antipsychotic augmentation in treatment-resistant OCD: double-blind, placebo-controlled studies.

Antipsychotic	Authors	Sample (N)	Trial duration (weeks)	Dose (mg/die)	Mean dose (mg/die)	Minimal length of SRI treatment before enrollment in the study	Results
Aripiprazole	Muscatello et al. 2011	40	16	15 (fixed-dose)	15 (fixed-dose)	12	Aripiprazole > Placebo
	Sayyah et al. 2012	39	12	10 (fixed-dose)	10 (fixed-dose)	12	Aripiprazole > Placebo
Haloperidol	McDougle et al. 1994	34	4	2-10	6.2±3.0	12	Haloperidol > Placebo
Olanzapine	Bystritsky et al. 2004	26	6	5-20	11.2±6.5	12	Olanzapine > Placebo
	Shapira et al. 2004	44	6	5-10	6.1±2.1	8	Olanzapine = Placebo (patients in both arms improved)
Paliperidone	Storch et al. 2013	34	8	3-9	4.94	8	Paliperidone = Placebo (patients in both arms improved)
Quetiapine	Atmaca et al. 2002*	27	8	50-200	91±41	12	Quetiapine > Placebo
	Denys et al. 2004	40	8	100-300	200	8	Quetiapine > Placebo
	Carey et al. 2005	42	6	25-300	168.8±120.8	12	Quetiapine = Placebo
	Fineberg et al. 2005	21	16	50-400	215±124	12	Quetiapine = Placebo
	Kordon et al. 2008	40	12	400-600	-	12	Quetiapine = Placebo
	Diniz et al. 2011#	54	12	50-200	142±65	8	Quetiapine < Placebo
Risperidone	McDougle et al. 2000	36	6	1-6	2.2±0.7	12	Risperidone > Placebo
	Hollander et al. 2003	16	8	0.5-3	2.25±0.86	12	Risperidone > Placebo
	Erzegovesi et al. 2005	20	6	0.5 (fixed-dose)	0.5 (fixed-dose)	12	Risperidone > Placebo
	Simpson et al. 2013	60	8	0.25-4	1.9±1.1	12	Risperidone > Placebo

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

drugs as a class can be considered a valid and first-choice treatment option in resistant OCD patients, especially when a partial response is evident and there is the need of further improving response without waiting for the time (12 weeks) necessary to evaluate the response to another first-line compound (in the case of a switch) (e.g. [47-49]). Not all antipsychotics proved to be effective in treating resistant patients (see Table III for antipsychotics studied, doses used and results versus placebo): aripiprazole and risperidone appeared effective in at least 2 positive RCTs, while only 1 positive study supports the addition of haloperidol and conflicting results are available for olanzapine (1 positive and 1 negative – probably biased – study) and quetiapine (more negative than positive studies). Concerning doses, 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. Approximately 50% of patients are expected to benefit from antipsychotic add on to SRIs [50].

At present, it is uncertain how long adjunctive antipsychotic treatment should be maintained once response is achieved: the discontinuation of the antipsychotic leads to an exacerbation of obsessive-compulsive symptoms in the vast majority of patients (83.3% within the 24-week follow-up)[51], suggesting the need to continue with the augmentation strategies in order to achieve remission and prevent relapses over the long-term. However, if such a 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 the metabolic ones [52].

In conclusion, we recommend prioritizing aripiprazole or risperidone add on to SRIs over other antipsychotics (olanzapine augmentation may also be effective, but only when the other two have failed), when such a strategy is used.

b. CBT addition to medication

The available evidence supports the sequential addition of CBT to SRIs for both OCD patients who respond to medications but still have residual obsessive-compulsive symptoms (1 positive randomized controlled study in adults) (this is a clinically relevant issue since only a minority of subjects accomplishes remission using a single treatment modality) [53] and for resistant patients (2 positive randomized controlled studies performed

versus a placebo psychological comparison – stress management training – and versus risperidone or placebo add on) [54,55]. Two other RCTs support the effectiveness of switching to medications after non-response to CBT [56,57].
For severe, treatment-resistant patients, several open-label or retrospective chart reviews support the efficacy of CBT delivered in residential settings or partial hospitalization programs: providing time-intensive treatment, based on delivering higher levels of treatment over a short time period, might be suitable for individuals whose immediate clinical improvement is important [34].

c. Switch to intravenous route of administration

A further approach in resistant OCD consists in changing route of administration, switching to intravenous therapy: this option is available only for clomipramine or citalopram. To date, only one study [58] investigated with appropriate methodology (randomized placebo-controlled study) whether IV clomipramine was efficacious for patients with OCD refractory to oral clomipramine. This controlled study demonstrated the significant superiority of IV clomipramine over IV placebo, indicating that IV clomipramine is an effective treatment for patients with OCD who have a history of an inadequate response or intolerance to oral clomipramine. Although no study specifically examined the efficacy of IV citalopram in non-responders to oral citalopram, clinicians might consider the use of intravenous therapy when patients failed oral SSRIs and hepatic first-pass metabolic effect is considered to contribute to resistance.

d. Switch to paroxetine or venlafaxine

Switching from clomipramine to SSRIs, or vice versa, or from SSRI to another SSRI, is a common strategy in clinical practice [28,59]. Only one controlled trial, however, supports the efficacy of this strategy: non-responders to prospectively administered venlafaxine or paroxetine responded to the switch to the other compound, with paroxetine being more effective than venlafaxine. The switch strategy is then recommended, to our opinion, only after the failure of antipsychotic or CBT augmentation, or when a first-choice compound showed no improvement, not even minimal.

e. Addition of medications other than antipsychotics to SRIs

The effectiveness of augmentative compounds other than antipsychotics in resistant OCD has been the subject of several double-blind studies, with promising results for some drugs and negative for others. A list of studies performed is provided in Table IV. All of the compounds that proved to be effective (namely pindolol and topiramate – only 1 positive RCT, memantine – 2 positive RCTs) should be considered as promising add-on strategies, although reserved for patients being refractory to other more evidence-based strategies [60]. From Table IV clinicians can find out which compounds not to use for resistant OCD patients.
Several controlled studies, moreover, investigated the efficacy of the addition of compounds other than antipsychotics *ab initio* in moderate to severe non-resistant OCD individuals (Table V). These strategies, although promising for improving the treatment outcome of OCD patients (by shortening response latency or increasing response rates), should be considered at the moment only for research purposes.

Table IV. Efficacy of augmentation with compounds other than antipsychotics in treatment-resistant OCD: double-blind, placebo-controlled studies.

Compound	Authors	Dose (mg/die)	Results
Lithium	McDougle et al. 1991 Pigott et al.1991	In range	Lithium = Placebo
Buspirone	Pigott et al.1992 McDougle et al. 1993 Grady et al. 1993	30-60	Buspirone = Placebo
Desipramine	Barr et al. 1997	125 ng/ml (plasma level)	Desipramine = Placebo
Inositol	Fux et al. 1999	1800	Inositol = Placebo
Pindolol	Dannon et al. 2000	7.5	Pindolol > Placebo
Gabapentin	Corà-Locatelli et al. 2001	Up to 3600	Gabapentin = Placebo
Clonazepam	Crockett et al. 2004		Clonazepam = Placebo
Naltrexone	Amiaz et al. 2008	100	Naltrexone = Placebo
Topiramate	Mowla et al. 2010 Berlin et al. 2011 Afshar et al. 2014	100-200 50-400 100-200	Topiramate > Placebo Topiramate = Placebo (> on compulsions only) Topiramate = Placebo
Lamotrigine	Bruno et al. 2012	100	Lamotrigine > Placebo
Memantine	Haghighi et al. 2013 Modarresi et al. 2018	5-10 20	Memantine > Placebo Memantine > Placebo
Riluzole	(Grant et al. 2014)* Pittenger et al. 2015	100 100	Riluzole = Placebo

** Children.*

Table V. Add-on treatment (ab initio) in moderate to severe OCD: double-blind, placebo-controlled studies

Compound	Authors	Mechanism	Dose (mg/die)	Results
Quetiapine	Vulink et al. 2009	antipsychotic	300-450	Quetiapine > Placebo
Granisetron	Askari et al 2012	5-HT3 receptor antagonist	1	Granisetron > Placebo
Ondansetron	Heidari et al. 2014	5-HT3 receptor antagonist	8	Ondansetron > Placebo
Celecoxib	Shalbafan et al. 2015	NSAID	200 x 2	Celecoxib > Placebo
Memantine	Ghaleiha et al. 2013 Farnia et al. 2018	NMDA receptor antagonist	20 10	Memantine > Placebo Memantine = Placebo
Riluzole	Emamzadehfard et al. 2016	Glutamate-modulating agent	50 x 2	Riluzole > Placebo
N-acetylcysteine	Paydary et al. 2016	Glutamate-modulating agent	2000	NAC > Placebo on YBOCS (not on response and remission)
L-carnosine	Arabzadeh et al. 2017	Glutamate-modulating agent	500 x 2	L-carnosine > Placebo
Gabapentin	Farnia et al. 2018	Glutamate-modulating agent	300	Gabapentin = Placebo

NSAID: nonsteroidal anti-inflammatory drug; NDMA: N-methyl-D-aspartate; NAC: N-acetylcysteine.

f. Use of brain stimulation techniques for treatment-resistant patients

Besides pharmacologic, behavioral, and neurosurgical approaches, different brain stimulation methods, including transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), deep brain stimulation (DBS), and electroconvulsive therapy (ECT), have been investigated in treatment-resistant patients with OCD [61,62], revealing positive results for otherwise intractable and treatment-refractory patients.

TMS and tDCS represent non-invasive brain stimulation techniques that have been investigated in patients with OCD with mixed results. A recent meta-analysis [63] including 15 RCTs (n = 483), most of which with small-to-modest sample sizes, found that active versus sham TMS stimulation was significantly superior for OCD symptoms. Nonetheless, stimulation targets and degree of treatment resistance show a wide variability across RCTs. There is less evidence in favour of the efficacy of tDCS versus TMS in OCD with a recent systematic review supporting cathodal compared to anodal tDCS in treating OCD [64].

With respect to more invasive somatic interventions, traditionally considered for more severe and treatment-resistant cases, ECT does not seem to produce any specific benefit in OC symptoms, being potentially useful only in cases of depressive and/or psychotic comorbidity [28]. On the other hand, levels of evidence for DBS efficacy in treatment-resistant OCD patients are more solid with a recent meta-analysis [65] including 31 studies (n = 116) showing a global percentage of Y-BOCS reduction at 45.1% and global percentage of responders at 60.0%. Stimulation targets were variable with most subjects implanted in striatal areas (anterior limbs of the internal capsule, ventral capsule and ventral striatum, nucleus accumbens and ventral caudate) and the remainders in the subthalamic nucleus and in the inferior thalamic peduncle.

Conflict of interests

The authors declare that there is no conflict of interests.

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Improved insight in first episode schizophrenic outpatients switching from oral to long-acting injectable aripiprazole: a cohort study

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Abstract

The concept of insight into psychiatric disorders is defined as the awareness of illness. Lack of insight is a well-established phenomenon in schizophrenia, with the estimated prevalence of poor insight ranging from 50 to 81%. Konsztowicz S et al. indicated, as the best-fitting model of insight in schizophrenia, five dimensions: 1) awareness of illness and the need for treatment; 2) awareness and attribution of symptoms and consequences; 3) self-certainty; 4) self-reflectiveness for objectivity and fallibility; and 5) self-reflectiveness for errors in reasoning and openness to feedback. Poor insight in schizophrenic patients has been linked to cognitive impairment, increased re-hospitalization rates, worse clinical outcome, psycho-social dysfunction, high risk for suicidality and poor compliance in treatment. Many naturalistic studies proved that long-acting injectable (LAI) antipsychotics improve symptoms, increasing adherence and reducing rates of relapse and hospitalization compared to oral antipsychotic formulations. Twenty-four schizophrenic clinically stabilized first episode schizophrenic outpatients in treatment with oral aripiprazole have been interviewed with the *Positive and Negative Syndrome Scale* (PANSS) at baseline (T0) and six months (T1) after switching to aripiprazole LAI. The difference between the average of total score of PANSS (T1-T0) was statistically significant, evidencing an improvement of general illness (Test t-student $t = -8.108$ ($df = 23$), $p < 0.001$). The improvement of the average score in the sample of three dimensions of PANSS (*Positive Symptoms, Negative Symptoms and General Psychopathology Scale*) (T1) *vs* (T0) was not statistically significant. Considering the item of the PANSS score that measures illness insight (G12), patients were categorized into two groups: good insight (score 1-2, which are in the normal range) and poor insight (score from 3 to 7). The difference of the average score of item G12 between T1 and T0 was statistically significant (Wilcoxon-Mann-Whitney test: -3.17; $p < 0.001$) evidencing an improvement of insight. This result on young patients (average 34.7 years) with normal IQ on insight and the total PANSS scores (T1 *vs* T0) supports the new literature data suggesting the use of LAI at the first-episode psychosis in order to improve the outcomes. Moreover, based on these results, it is hypothesized that the good relationship between efficacy and tolerability (effectiveness) of aripiprazole LAI in long-term treatment leads to a full compliance of the patients. So the authors argued that the improvement of insight would depend on a balanced control of symptoms that allows patients to be clinically stable and at the same time in contact with their own internal world. Finally, the results of this study, suggest that a full and continuous treatment of symptoms could improve insight and consequently functional outcomes and voluntary adherence to pharmacological therapy.

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Introduction

The concept of insight into psychiatric disorders has long referred to the awareness of illness. In 1882, Pick [1] defined the insight as a patient's recognition of "*the pathological aspect of his mental processes, or some part of them, more or less clearly*". Pick hypothesized that insight always involves various *degree of lucidity*, referring to the weakest form as *illness-feeling*, and naming the strongest full-fledged form of insight as *illness-insight*, denoting a cognitive process of conscious reflection and reason.

Insight is a complex construct that entails several dimensions, such as the awareness of specific symptoms and the perceived need of treatment.

According to contemporary models, insight depends on the interaction of neurocognitive [2], social-cognitive and meta-cognitive abilities [3], which form the basis for the development of a coherent autobiographical narrative. Moreover, lack of insight is considered as a shield mechanism against the painful psychotic experience [4]. Konsztowicz S et al. [5] selected, as the best-fitting model of insight in schizophrenia, five dimensions: 1) awareness of illness and the need for treatment; 2) awareness and attribution of symptoms and consequences; 3) self-certainty; 4) self-reflectiveness for objectivity and fallibility; and 5) self-reflectiveness for errors in reasoning and openness to feedback.These components were distinguished between clinical (components 1-2) and cognitive insight (component 3-5). Cognitive insight is considered, nowadays, a malleable target for intervention. Particularly the first aspect is related to awareness of the mental disorder and beliefs regarding the need for medication and hospitalization (*Illness & treatment*). The second one pertains to awareness and attribution of symptoms and consequences of the disorder, as well as attribution or explanation of the illness itself (*Symptoms & consequences*). The third was analogous to the self-certainty subscale of the BCIS (*Beck Cognitive Insight Scale*) [6], or a tendency to be overconfident (*Self-certainty*). The fourth point relates to a willingness to be objective about one's judgments and to acknowledge one's fallibility or likelihood of making errors in judgment. These capacities require self-reflection6 (*Objectivity & fallibility*). The last point involves self-reflection, but relate more to recognizing errors in reasoning and demonstrating an openness to feedback from others. (*Reasoning error & feedback*).

Lack of insight is a well-established phenomenon in schizophrenia, with the estimated prevalence of poor insight ranging from 50 to 81% [7 8]. Poor insight in psychiatric patients has been linked to cognitive impairment, increased re-hospitalization rates, worse clinical outcome, psychosocial dysfunction and poor compliance [9]. The *Clinical Antipsychotic Trials of Intervention Effectiveness* (CATIE) study, a nationwide public health-focused clinical trial of antipsychotic medications, has examined the correlation between insight and poor compliance and they showed how patients with poorer insight, who were most likely to discontinue treatment, also had relatively more severe levels of psychopathology [10].

It has been proposed that the insight also have a bidirectional relationship with social function. Consistent with this, better clinical insight was correlated with better personal and social skills [11] and prosocial behaviour [12] and could predict higher levels of community function, including frequency of social contact and perceived social support [13] and as consequence the capacity to be socially connected [14-17].

On the other hand, poor insight might lead to a worse coping pattern [18], higher level of psychotic symptoms [19], and basic self-disorders [20].

That leads to the conclusion that patients may have different degrees of insight according to the phases of illness [21 22]. Furthermore, many studies demonstrated a strong correlation between poor insight and depression especially linked with psychotic features and feeling of hopelessness, paranoid delusions and ideations [23-25].On the contrary, patients with good insight are at higher risk to be depressed if they have lower socioeconomic status, more severe illness and worse service engagement. Structured, multicomponent psychotherapy might be useful to contrast the onset of depression, and ultimately promote patient's well-being [16].

Many naturalistic studies have demonstrated that long acting injectable antipsychotics improve symptoms while increasing adherence and reducing rates of relapse and hospitalization, compared to oral antipsychotic formulations [26 27]. The efficacy, safety, and tolerability of aripiprazole once-monthly 400 mg (AOM 400) to treat acute exacerbation of psychotic symptoms in adult patients with schizophrenia, has been widely described [28]. Aripiprazole once-monthly 400 mg was superior to placebo based on change from baseline to week 10 in *Positive and Negative Syndrome Scale* (PANSS) [27]. Zahinoor Ismail and al. [29] showed as in patients experiencing acute schizophrenia exacerbation, treatment with AOM 400 and concomitant oral aripiprazole in the first 2 weeks was rapidly efficacious in many aspects of the disease analysed with PANSS. Moreover, treatment with AOM400 had significant results for both short- and long-term outcomes [29]. In our paper we argue that switching from oral aripiprazole to AOM400 in order to treat schizophrenic outpatients could contribute to increase their awareness of the disease and consequently their compliance.

To our knowledge the insight is not an aspect that has been analysed as the core of the compliance and the quality of life of patients in any clinical trial with LAI.

Subjects and methods

Recruitment took place in between 2015 and 2017 among outpatients of the Mental Health Department of Chieti, Italy. Inclusion criteria were a diagnosis of schizophrenia, single episode (FEP) according to the Structured Clinical Interview for DSM-IV (SCID-I-P); age between 18 and 65 and clinical stability, defined as the absence of variation of antipsychotic drug therapy or hospitalization for symptom recrudescence in the 3 months before recruitment. Exclusion criteria were: neurologic disorders; history of alcohol dependence or substance abuse in the past 6 months; moderate or severe mental retardation; recent history of severe adverse drug reactions, such as neuroleptic malignant syndrome; inability to provide informed consent.

Twenty-four schizophrenic clinically stabilized outpatient

(n = 13 male, n = 11 female - mean age: 37.4) in treatment whit oral aripiprazole (10-30 mg/die) were interviewed with the *Positive and Negative Syndrome Scale* (PANSS) at baseline (T0) and six months after the switch to aripiprazole LAI once-monthly 400 mg (T1). The PANSS is a 30- item, 7-point severity scale designed to measure positive and negative symptoms as well as general psychopathology among patients with schizophrenia. The PANSS interview analyse three domains of symptoms: positive symptoms, negative symptoms and general pathology. Each item can berated from 1 (not present) to 7 (extreme). Moreover, the *Scale to Assess Insight* (SAI), the *Scale to Assess Insight - Expanded* (SAI-E Insight) and the *Treatment Attitudes Questionnaire* (ITAQ) were perform.
The interviews were all conducted by experienced and trained clinicians.

Results

Our sample is composed by 24 patients (mean age 34.7) at first episode psychosis. All our patients had a normal IQ and they were clinically stable, in treatment with oral aripiprazole. The difference between the average of total score of PANSS (T1-T0) was statistically significant, evidencing an improvement of general illness [Test t-student t = -8.108 (df = 23), p < .001]. Instead, the difference between the average score in the sample of three dimensions of PANSS (*Positive Symptoms*, *Negative Symptoms and General Psychopathology Scale)* (T1) *vs* (T0) is not statistically significant, according to the fact that the sample was composed by patients with stabilized symptoms (POS_T1 *vs* POS_T0, t = – 0.396 (df = 23), p = 0.695; NEG_T1 *vs* NEG_T0, t = – 0.273 (df = 23), p = 0.787; GPS_T1 *vs* GPS_T0 t = – 0.613 (df = 23), p = 0.546).
Since the main outcome of this study was to analyse the change in insight, we further considered the G12 item of the PANSS at T0 and T1. The difference between the average score G12 (T0) *vs* G12 (T1) is statistically significant highlighting a significant improvement of insight in schizophrenic outpatients when switching from an oral to a long injection formulation aripiprazole in 6 months of LAI therapies (*Test di Wilcoxon Z*: – 3.17; p < 0.001). In the meanwhile, the difference between the average of total score of PANSS (T1) *vs* PANSS (T0) is statistically significant, highlighting a significant improvement of general illness in outpatients who switched from an oral to a long injection formulation aripiprazole after 6 months of LAI therapies [Test t-student (T1 *vs* T0) t = – 8.108 (df = 23), p < 0.001].

Discussion

In this study we tried to select a sample of patients well stabilized, after a first episode of psychosis, with normal IQ. In fact, literature reports that early treatment in firs episode psychosis leads to a better clinical outcome [30,31]. Moreover, a good insight is probably linked to a good cognitive insight and a better cognition of illness [6].
According to this statement, our sample was similar considering age and clinical features. All patients were stabilized with at least 3 months of oral aripiprazole (mean dose 15-20 mg), other treatments were allowed, mainly benzodiazepines for insomnia, but the pharmacological treatment had to be stable for at least 3 months. We did not analysed differences among social and economic status or level of instruction even though that could represent a minimal bias.
Aripiprazole LAI is well known to be well tolerated, with the same efficacy and effectiveness of oral aripiprazole [32], even in patients with resistant schizophrenia [33]. Moreover, compliance was guaranteed because they had to be visited, once per month necessarily, by a specialist.
No one complained important side effects and no one decided to quit the therapy proposed due to collateral effects or intolerance to treatment, witnessing the good tolerability and safety of aripiprazole.
All patients declared an improvement in their quality of life and they felt more aware of their illness.
In literature there is not a trial focused on insight improvement switching from an oral to a long acting antipsychotic, except for one clinical trial by [34]. They analysed many dimensions of pathology in schizoaffective and schizophrenic patients treated with risperidon LAI, finding a good improvement in symptoms and insight as well. So the authors hypothesized that, while the symptoms are well controlled with a stable therapy, the patient could work on his internal world, more aware of his illness but trying to reach a better quality of life. In particular, in our sample, the average of patients at T0 recognized that they had a psychiatric disorder but clearly underestimated its seriousness, the implications for treatment, or the importance of taking measures to avoid relapse. At T1 same sample was just above the upper extreme of normal limits of adequate of their awareness of the disease.
Gaining insight during treatment was associated with higher compliance, reduced risk of suicide and better outcomes, underlining the need to monitor insight over time and tailor interventions according to symptoms and phases of illness [35].
According to the scores of the G12 (*Lack of judgement & insight*) item of PANSS, patients were categorized into two groups: good insight (score 1-2, which are in the normal range) or poor insight (score from 3 to 7). Even though this is only one single item, strong correlations were found with other psychometric tests that investigate the insight such as the *Scale to Assess Insight* (SAI; r = 0.88), *Scale to Assess Insight - Expanded* (SAI-E; r = 0.90), or the Insight and *Treatment Attitudes Questionnaire* (ITAQ).
The improvement in the score of the G12 item was statistically significant, confirming the hypothesis of the authors about the importance of an early intervention and a good compliance.
Limitations of the study were the small sample size, the lack of a control group with oral aripiprazole or with another antipsychotic and probably the short period of observation. Anyway our sample reflects a real world situation since all patients were recruited in a public health care service.

Conclusions

On the basis of the results it is possible argue there is a two-way relationship between a good insight of illness

and a full adherence to treatment with aripiprazole. This may depend on the good relationship between efficacy and tolerability (effectiveness) showed by aripiprazole in long-term treatment [28].

So we argued that the improvement of insight would depend on a balanced control of symptoms that allows patients to be clinically stable and at the same time in contact with their own internal world. We also believe that the improvement of insight must be pursued already at the first episode of illness both with appropriate treatment and with soothing psychotherapeutic and psychoeducational interventions. Finally, the results of this study, suggest that a full and continuous treatment of symptoms could improve insight and consequently functional outcomes and voluntary adherence to pharmacological therapy. Further studies, with bigger sample size and a control group, are needed to confirm these hypothesis.

Conflict of interests

The authors declare that there is no conflict of interests.

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General and peculiar aspects of psychiatric certification

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Abstract

The certification activity, especially in the psychiatric field, takes a quite peculiar meanings and characteristics, also due to the reflexes that it can determine on the therapeutic relationship with the patient and for the consequent of medical-legal implications.
The authors propose a review of the literature and the regulations concerning the methods and purposes of the certifications in psychiatry and hope for the formulation of suitable guidelines to standardize the processes.

Introduction

Those who choose the medical profession should have the constant awareness that every act, however simple and banal it may seem, is fraught with ethical, deontological and medico-legal implications. To these implications is not eluded the certification activity which, especially in the psychiatric field, takes on particular meanings and characteristics. The psychiatrist, more than any other specialist, in the act of drawing up a certificate should always maintain full awareness of the limits of his knowledge, of his forecasting abilities and, even more, of the potential iatrogenic effect of any diagnostic and prognostic hypothesis even necessary as they are aimed at the affirmation of certain rights, if negative they can negatively influenced life of the patient and the course of the illness, inducing in the same incapacity, inactivity and social deresponsibility [1]. Among other things, it would be desirable for authorities and institutions to develop national and international guidelines that suggest a unified procedure for drafting the certificate in order to minimize the ambiguity that the psychiatrist is inevitably faced whenever it is required to certify [2].
The possibility of ascertaining facts whose demonstration has legal and / or administrative significance both for the company and for the individual entity and to issue a certification derives from the general principle that the qualification to exercise a given profession involves the recognition of specific technical competence in that field [3].
The activity of the health professional does not end, therefore, at the time of clinical-diagnostic evaluation, but extends to very different tasks that materialize a real administrative continuation of the medical act in order to witness the recurrence of conditions possibly produced from particular consequences foreseen by the law.
It is therefore a primary characteristic of the medical profession *the duty to certify* that is achieved through the drafting of the certificate, the undoubtedly most widespread form of documentation of medical activity [4]. If by certus we mean what is true, real, concrete, for the healthcare professional this concept of truthfulness can only correspond precisely to what is objectivable by him and therefore clinically verifiable [5]. According to Gerin (1964) *"the certificate is the written act which declares to be in accordance with truth facts and conditions of a technical nature for which it is intended to prove existence"*; that is, written testimony on technically evaluable circumstances and facts, the dem-

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onstration which can determine the assertion of particular subjective rights provided for by law, or produce certain consequences for the individual and society, having legal and / or administrative relevance. From this we can see its great importance both on the deontological level and on the more properly juridical one, placing itself as an ideal link between the personal and private sphere of the patient and the social sphere [4].
The issue of a certificate by the physician takes place at the request of the patient, visited or otherwise interested or, eventually, by the legal representative (parents for the minor, guardian for the interdict etc.) and its content must be limited to what the applicant intends to make manifest.

Certificative activity and relationships with the judicial authority

According to the penalistic qualifications provided for by our penal code, the health care professional can take on the role of public official (Article 357 of the Criminal Code), in charge of a public service (Article 358 of the Criminal Code) or a service of public necessity (Article 359 of the Criminal Code). Depending on whether it is attributable to one of these three legal figures there will be different consequences as regards the configurability of the criminally relevant facts, the gravity of the offenses committed and the applicability of ancillary penalties. The "minimum" criminal qualification referable to any health care professional is that of "a person performing a public necessity service"; therefore, in the performance of his duties, the doctor is never considered (criminally) an ordinary person.
For the doctor who works in a national healthcare system (SSN) or who, in any case, performs the role of public official **public official** (Article 357 of the Italian Criminal Code) during the course of his duties, the refusal to certify could constitute the crime of "refusal or omission of official deeds "(Article 328 of the Criminal Code). According to the Court of Cassation, they also have the status of a public official: "the ASL outpatient specialist doctor" (Cassation Section VI, 20 January 1989); "The doctor who exercises his professional activity in the care of a clinic affiliated with the Ministry of Health" (Cassation Section V, 21 January 1981); "The health professionals who carry out their professional activity in the context of and in the care of a civil hospital"; "The medical director of a hospital because its organizational function involves powers of authority and direction"; "The sanitary who proceeds to the fiscal visits" (Cassation Section VI, 1 April 1980); *"The doctor who ascertains the existence of the pension requirements, the one who works as an expert or technical consultant, the medical doctor at the time when he ascertains death"; "The doctor who draws up a certificate of fitness to drive"* (Cassation Section VI, 20 January 1989).
Compared to the public official, the professional has greater discretion in the performance; these, in fact, in his legal role as an **essential public service** (Article 359 Criminal Code), has different constraints and, without prejudice to ethical and deontological ones deriving from the medical profession itself, in the event of illegal acts its function involves different penality from what is provided for the public official. Some certificates issued by freelancers (for example, the sickness insurance certificate for private insurance) are sometimes referred to as "private papers".
In current legislation it is possible to distinguish between **statutory certificates**, which the citizen has the obligation to show if he intends to assert his right, and **non-mandatory certificates** if they are requested on the basis of an interest of the assisted person to be presented to public or private bodies order to document the state of health. The obligation nature, therefore, is to refer to the existence of the certificate itself which is necessary to start a specific course or administrative procedure, while the doctor cannot and must not refrain from issuing the certificates requested by the patient.
Also for the doctor those certificates which he must send on his own initiative and not at the request of a private person are obligatory, on the basis of a duty that the law puts on the health care professional.
The acts of required information (**complaints**) have some fundamental characteristics: they derive from an unavoidable legal provision; they start at the initiative of the complainant (and not at the request of the patient); they concern facts of public interest and therefore are aimed at the social protection of the community and not at safeguarding the interests of the individual; they are intended for a public administration and may involve criminal penalties (generally of a violation type). Then, depending on the administrative body concerned institution, the complaints to which the doctor is held are classified into three main types: *administrative*, to be addressed to the Mayor or to the Civil Status Office of the municipality, concerning the activities of the public administration (eg certificate of birth assistance, necropsy certificate, report of causes of death); health, aimed at protecting hygiene and public health, in general in relation to prophylaxis activities (eg, reporting of infectious and diffusive diseases, reporting of venereal diseases, reporting of occupational diseases, reporting of mandatory vaccinations, etc.); *complaints* to the Judicial Authority, represented by the report and the report (or report of crime).
The report, in particular, is the report that the operator of a health profession who has provided his service in cases that may present the characteristics of a crime for which he must proceed automatically, must present to the judicial authority or other authority and has the obligation to report [4].

According to the Article 365 of the Criminal Code in which is expected that the health care professional (even in a profession) formulates a judgment of possibility on the existence of a punishable offense under the law, according to Article 361 of the Criminal Code "*The public official who omits or delays reporting to the judicial authority, or to another authority that has the obligation to report it, a crime of which he has been informed in the exercise or because of his functions, is punished with a fine by sixty thousand to one million lire ... The preceding provisions do not apply if it is a crime punishable by a lawsuit against the injured party* ". In the case of the report, therefore, explicit reference is made to having information about a crime that can be prosecuted ex officio, thus extending the mandatory nature of the report also to fines (less serious crimes,

punished with arrest or fine) . Furthermore, no exemption is envisaged (as required, instead, for the report in the case in which the assisted person is exposed to criminal proceedings) so that the healthcare professional who performs the function of public official is always obliged to report. In addition, the report must be presented as soon as possible and it is sufficient that the health care professional is aware of the crime, as its performance is not necessary.
Outside the mandatory situations described above, the doctor can, however, maintain a certain discretion in the bargaining of the demand that often requires clarification on what can be certified or not. Specifically, **the issue of a certificate can and must be refused**: if untruthful content is requested (ideological falsehood: Article 480 criminal code); if the certification requires skills that the healthcare professional does not possess; if the certificate is required in a free-professional context, since it is the responsibility of the NHS (eg, issuing a driving license or procedures concerning the IVG beyond the ninetieth day).

Certificate failure

The penal code provides for a long series of articles (from 476 to 493-bis) which govern the false document. The legislator distinguishes between **material falsehood and ideological falsehood**. This distinction is closely connected to the double meaning that the concept of false can assume, that is, not genuine or untruthful; in the first case we will speak of false material, in the second of false ideology.
More precisely, the **false props**, excluding the genuineness of the document (where genuine means that document which actually comes from the person who appears to be the author and has not undergone modifications, of whatever kind they may be, after its formation), it can come in two forms: counterfeiting, if the document is written by someone other than the one who appears to be the author; and alteration when, on the other hand, the document drafted by the person appearing as an author has made changes of any type (additions, deletions) in a post-editing period. Otherwise, the **ideological false** relates to the content of the act, taking the form of a document that is not counterfeit or altered, but containing false statements by its own author, which do not correspond to the truth, which the legislator expresses with the term “false testimony” [6].
The offences of false related to certification vary according to the acts in which the certifying authority of the physician takes place (certificates, report, complaint, recipe, report, evaluation and technical advice, etc.) which may have a different legal nature (private writing, deed public or administrative certification) and consequently different criminal protection, due to the juridical qualifications that the doctor can cover according to the public or private nature of his functions. For example, the medical record, the operating room register, the first aid register, the certificate of fitness to drive, the death certificate are peacefully recognized as public documents; those acts, in essence, in which the administrative aspect prevails, that is the public incidence that the act takes with respect to the professional activity of the doctor.
The doctor with public functions is liable for material falsehood (Article 476 of the criminal code in public deed and Article 477 of the criminal code in administrative certification) if in the drafting of the certificate he commits alteration or counterfeiting through erasures, abrasions, subsequent additions aimed at making the conditions required for the its validity. In the event of false material, the professional responds to the Article 485 of the Criminal Code in which penalties are less severe than those reserved for doctors with public functions.
The doctor with public functions is liable for ideological falsehood (Article 479 of the Criminal Code in public deed and Article 480 of the criminal code in administrative certification) if the diagnostic judgment expressed in the certificate is based on facts, not adhering to the truth, regardless of whether they are explicitly declared or implicitly contained in the judgment itself (Cassation Section VI, 24 May 1977). The doctor who carries out free-professional activities in the event of ideological falsehood responds, instead, to the Article 481 of the Criminal Code: even in this case the penalties provided for are less severe. In any case, the “fraud” is an indispensable condition for the crime of ideological forgery to take shape. In fact, our jurisprudential system does not provide for the crime of negligent certification, that is the case in which, in good faith, the doctor has certified false data (Cassation Criminal Section V, 31/01/1992). In particular, a clear distinction is made between false and erroneous diagnosis: false is that certification which is based on objective premises that do not correspond to the truth, while it is wrong (and therefore without fraud) if the interpretation given to justify the clinical judgment is unreliable (Cassation Criminal Section V, 03/18/1999).
The ideological falsehood cannot be attributed to the normal citizen being a crime proper of the public official and / or person in charge of the public service. The citizen who makes false statement is instead punishable pursuant to Article 374-bis of the Civil Code (with greater penalties if the offense is committed, once again, by a public official, in charge of a public service or a healthcare professional).

Certification in psychiatry

Psychiatric certification is a specialized medical certification related to the mental state of an individual; as such, it assumes the same legal and medical-legal significance attributed to all other medical certification activities, thus being subject to the same legislation [7,8]. As in the other disciplines of medicine, even in psychiatry the certification of any condition must always and in any case be preceded by a suitable clinical evaluation of the patient which must be carried out remembering that the purpose is, however, of a medical-legal nature, since the subject of the certificate is not the suffering of the patient, but the individual himself as a juridical person and, therefore, depository of rights and duties. Among other things, it is essential to try to maintain a neutral position in order to identify the elements necessary to satisfy the purposes for which the certificate is requested and produced, setting aside interpretations or personal considerations and avoiding, above all, that the certificate can become a tool for bargaining

with the patient. In doubtful cases (eg when the patient is not well known by the certifier) it may be useful to spend more time collecting more detailed information, using, if necessary, the consultation of other operators who know the patient better.
In any case, psychiatric certification is essentially based on the detection and quantification of ongoing psychopathological alterations, or on the explicit confirmation of their absence. To this end, an accurate psychic physical examination and a careful medical history are in themselves sufficient to identify / exclude the psychopathological alterations in question. However, in some circumstances that are more difficult to find, for the formulation of a correct categorical diagnosis (or even simply to document the recovery from a previous disease condition), it may be necessary to perform a psychodiagnostic deepening through the use of psychometric tests and / or instrumental examinations. In the presence of linguistic barriers and / or significant cultural differences, it will instead be possible, always with the user's consent, to use interpreters and cultural mediators, having then the care to report the assessment methods in the document drawn up and highlighting any difficulties encountered. It is also always possible, once the condition of the disease has been ascertained, to express an opinion regarding the possible consequences on the level of functioning and on the skills that can be highlighted, except for all those certifications subject to the examination of specific commissions (for example, carrying weapons, disability, driving license), in which case it would be more appropriate to limit oneself to clinical evaluation only, leaving the conclusions to the dedicated committees.
Finally, it is admitted that the doctor can issue a "retrospective" certificate based on memory (historical certificate), better if supported by documents or clinical evidence notes found by the same healthcare professional at the time which the certification refers.
Generally the psychiatrist is required two main types of certification aimed at documenting, respectively: absence or ascertainment of pathology compatible with the ability to obtain authorization to carry out certain activities; existence of pathology so that the affected person can exercise a right (pension, social security, etc.).

As already mentioned, psychiatric certifications present elements common to every other medical certificate, but there are specific and completely peculiar characteristics such as:

- the problem of objectivity;
- the fact that sometimes not only a diagnosis or an opinion on the present is requested, but a real forecasting judgment on possible future consequences;
- the "possibility" of issuing certificates not on request, but in the interest of the patient;
- the possibility of separating clinical functions from certification (and medico-legal functions in general) due to the very serious implications that certification often creates for the patient.

With regard to the first point, it is well known that it is impossible to document almost all psychiatric symptoms with instrumental and / or laboratory investigations. As repeatedly stated, the certificate must attest the truth, or what was directly reported by the doctor, inevitably affected by a series of variables that can be modified based on the quality and context of the patient medical relationship, the attention and availability of the psychiatrist, but also of the insight and patient "honesty". Often, the problem of lack of objectivity is related not only to the possible simulation by the patient but also to the aura of suspicion that surrounds psychiatric diagnoses, due to the stigma surrounding mental illness [9]. All these difficulties cannot, however, exempt the psychiatrist from a rigorous and categorical description of the symptoms that can actually be found. In the absence of different criteria of objectivation it can perhaps be said that the certificate should contain a description of the average and repeatable case, corresponding to what could be written by different specialists compared with the same case [10].
Related to objectivity is the problem of lexicon: psychiatric certification is often the translation and reduction of a personal history and an intersubjectivity in psychiatric terms and codifications. If for the physician this terminology can involve some diagnostic labels to refer now to one patient now to another, for the assisted, instead, even a single term or a simple expression can take on a meaning of irreversibility and be lived as if they were a final judgment. Therefore, for the psychiatrist there is the problem of "how to say" in respect of the truth. It is also necessary to consider that in psychiatry a diagnostic label can change as the diagnostic system used changes, the environment in which the patient lives or that of the doctor who is treating him [11].
Among other things, more and more frequently, not only is the psychiatrist required the drafting of certificates to describe an objectivity present, but also to attest the possible and probable future consequences of such objectivity on the reality of life of the patient. Typical, in this case, the certificate required for the issue of the driving license or the license to carry firearms, whose substantial question (underlying the apparently simpler formal license) requires a future assessment of the probability that the patient's psychopathological problems manifest with inappropriate behavior. It is a question of formulating a completely different judgment from the ordinary prognosis that in psychiatry introduces in the reasoning such and many variables as to make it in practice extremely difficult and unreliable [12].
With regard to the third criticality, it is appropriate to consider that the psychiatric patient, especially if suffering from a serious pathology, can incarnate a "weak" individual that third persons (eg family members), even without having a real legal protection, want to protect with the certification. In some cases the patient opposes the release of his health certificate, losing or not obtaining the benefits of which he would also be entitled to an economic nature, and the request made by a family member involves difficulties that cannot be easily managed by the health care provider who any case should operate only if authorized by the patient and in compliance with professional secrecy. In fact, both from an ethical and a medical-legal point of view, no document should be prepared at the request of third parties, even if the attendant himself deems it useful

and “to protect” the patient: therapeutic alliance and privilege of the doctor-patient relationship must be privileged in any case, even to the detriment of the interest deriving for the patient from the execution of a single procedure. Therefore, all the certifications on the conditions of the assisted or visited person, released to third parties, potentially constitute a serious violation of professional secrecy. If the certification takes place within a continuous therapeutic relationship, it is, in fact, a fundamental moment, not to be separated from the relationship itself. Considering, in fact, its possible implications on the patient’s life, both positive (obtaining benefits) and negative (limitations of various kinds), certification cannot be considered a mere bureaucratic act, having a strong impact on the therapeutic relationship and on its evolution. Within the doctor-patient relationship, however, problems may arise due to the more or less conscious inclination of the psychiatrist to draw up a certificate that complies and is convenient to the therapeutic project and the patient’s expectations, as well as the risk of complacency for treatment purposes. When, on the other hand, the certification represents the only act of the relationship between doctor and patient, as in the case of a specialized assessment requested by the patient for forensic purposes, one can easily incur in those peculiar critical issues, concerning diagnosis, prognosis and absence of objectivity, without counting the risk of a relationship in which, on the contrary, a suspicious and inquiring attitude of the doctor corresponds to a defended and manipulative behavior by the patient.
Being able, therefore, a psychiatric certification entail potential, and often real, negative effects on the therapeutic relationship, the possibility (sometimes the necessity) of separating the clinical functions from those of the certifier should always be evaluated. This separation should be absolute at least in the case of official medico-legal assessments, technical consultancy and expert assessments; in fact, if it is true that the carer is the one who knows the patient best, for the same reason it is equally true that he will hardly be able to observe his patient with a different point of view, being able, among other things, to run the risk of reaching conclusions conflicting with its therapeutic action.

Examples of psychiatric certifications

• Certificate of assessment proposal or mandatory medical treatment - The current rule provides that any doctor can request the mandatory health check if the subject refuses any evaluation contact (ASO) or make a proposal for mandatory health treatment (TSO) by certifying the existence of psychic alterations such as to require urgent therapeutic interventions, the impossibility of practicing the same treatments in extra-hospital conditions and the refusal of the same treatments by the patient, after the same has been adequately informed of the conditions in which it is found and of the need for therapy. In both cases, including the validation of TSO, the legislation provides that the intervention is carried out by the competent public health facility (law December 23, 1978, No. 833).

• Certificate on the ability to express consent or denial of diagnostic and / or therapeutic procedures - To assess the possession of mental faculties that make a subject able to express a valid informed consent or refusal to undergo diagnostic and / or therapeutic procedures , it is necessary first of all to verify the degree of awareness of the disease on the part of the same, as well as the level of understanding of the information prior to consent. In addition to the assessment of mental status, the clinical examination must also make use of any laboratory-instrumental data that can document the presence of organic elements capable of compromising normal mental processes (toxic and / or dysmetabolic states). In particularly serious cases, if the conditions are met, the state of necessity may be present (Article 54 Criminal Procedure Code); outside these circumstances, the temporary appointment of a guardian may be considered.

• Civil disability - The certification is aimed at defining the psychiatric diagnosis and the user’s level of functioning starting from the clinical evaluation and considering the contextual presence of any organic comorbidities; in fact the disability can also derive from the presence of more concomitant pathologies. The revaluation of the invalidity percentage is done periodically. In these cases, if significant variations do not emerge, a medical history update is sufficient.

• Advice aimed at ascertaining the psychosexual conditions of the person concerned - according to current legislation to rectify the assessment of sex completed at the time of birth and thus reaching a new “attribution”, the Italian legislation is based on “changes occurred in the sexual characteristics ”, understood in a physical sense, and on the conviction of the subject to belong to a sex different from the one ascertained. This last requirement provides for the acquisition of a consultancy intended to ascertain the psychosexual conditions of the interested party (Rules on the subject of rectification and attribution of sex - L. April 14, 1982, n. 164). If a subject asks to undergo medical and surgical interventions with definitive effects, the clinical evaluation, supplemented by the psycho-diagnostic evaluation, must be particularly thorough and include a preparatory program aimed at changing and acquiring the new gender identity through an adequate psychotherapeutic process. .

• Certificates of psychophysical suitability at the port of rifle for hunting use and at the port of arms for personal defense use - The Ministerial Decree of 28 April 1998 identifies the minimum psychophysical requirements for the issue and renewal of the authorization to carry guns for hunting purposes, and to carry weapons for the sport of sport shooting or for personal defense (Articles 1 and 2). According to the aforementioned decree, for the issue of certification of suitability to carry weapons, in addition to the minimum, purely physical, auditory, visual, neurological and motor requirements,
the presence of “mental, personality or behavioral disorders must be excluded. Specifically, there must be no dependence on drugs, psychotropic substances and alcohol, as well as the occasional intake of drugs and the abuse of alcohol and / or psychotropic drugs “. Therefore,

the psychiatrist has the task of excluding or confirming the presence of the clinical conditions identified in articles 1 and 2. In addition to a detailed psychic and medical history examination, in these cases it is fundamental to define the subject's lifestyle, his tendency to be irritable or impulsive, that is all those personality characteristics (to be understood in terms of functional individual and socio-working modalities with respect to oneself and the environment) that could be ill-reconciled with the suitability to carry weapons. In this sense, even information that is not strictly clinical in nature, such as, for example, the suspension of the driving license due to exceeding the blood alcohol limits, although occasional event, may prove to be unjust to express an incompatibility judgment with the firearms . Hence the need to converge more information, favoring the integration of different professional skills to provide an assessment as comprehensive as possible [13].
In doubtful cases it may be useful to make use of psychodiagnostic assessments of the personality and / or of a specialized consultation of the Ser.D. for what concerns the more strictly toxicological or alkological aspects. It is therefore a complex evaluation with important medical-legal implications. In fact, in case of incompetence and negligence, the certifying doctors could answer for the hetero-harmful acts committed by the patient in possession of the firearms. Similarly, the user who declares the forgery or deliberately omits significant anamnestic information commits an offense punishable ex officio (Articles 495-496 of the Criminal Code, "False statements") which, as such, should be reported by the health care professional if the right exists cause to disclose professional secrecy.

• Certificate of suitability for driving motor vehicles - Article 330 of the D.P.R. 495/92 and the article n. 119, paragraph 4, of the Highway Code (C.d.S.) delegate to the local medical commission the competence of the evaluation on the psycho-physical suitability to the guide. According to the Article 320 of the C.d.s. "The driving license must not be issued or confirmed to candidates or drivers who are affected by mental disorders due to illness, trauma, post-surgery surgical procedures on the central or peripheral nervous system or those suffering from severe mental retardation or who suffer from psychosis or of personality disorders, when such conditions are not compatible with driving safety, except in cases that the local medical commission may evaluate differently, making use, where appropriate, of specialist advice at public facilities ". The driving license must not be issued or confirmed even to those who are in a state of current dependence on alcohol, narcotics or psychotropic substances or to people who habitually consume substances capable of compromising their suitability to drive without danger. In the case of a previous dependency of the local medical commission, after having assessed with extreme caution the risk of a possible relapse using appropriate clinical and laboratory assessments, also through the request of a specialist consultation, it will be able to express a favorable opinion or contrary to release. In all cases so far discussed, the validity of the license cannot exceed two years. The same principles apply to confirmation and revision.
In summary, a specific certification for the driving license must include: a diagnosis, the current psychopathological status, the possible therapy taken and the adhesion or not to the treatments; any toxicophilic behaviors of which one is aware must be certified by the competent services (Ser.D. and Alcoholic Services).

• Voluntary interruption of pregnancy (IVG) - The law 194/78 "Norms for the social protection of maternity and on the voluntary interruption of pregnancy" foresees two different types of attitude of the sanitary with regard to the interruptions of pregnancy depending on of the time of the same, setting the watershed 90th day of gestation. While for IVG within the first ninety days the doctor (specialist, trust or counseling), at the request of the expectant mother, issues a certificate attesting to the state of pregnancy and the request to interrupt it, based on Article 6 of the same law, the IVG after the first ninety days can be practiced exclusively on the occurrence of two conditions, namely: a) when the pregnancy or childbirth involve a serious danger to the life of the woman; b) when pathological processes are ascertained, including those relating to significant anomalies or malformations of the unborn child, which cause a serious danger to the physical or mental health of the woman. The following article postulates that the pathological processes contemplated in the Article 6 are ascertained by a doctor of the obstetric-gynecological service of the hospital in which the intervention is to be carried out which, if deemed necessary, can avail itself of the collaboration of specialists.
The psychiatric evaluation to ascertain the psychic danger must first of all be based on the investigation of the risk factors, as well as on the finding of an objective symptomatology detectable with common parameters. To this end, an accurate psychic examination, with a detailed collection of anamnestic data, must be accompanied by an assessment of the social conditions that may negatively affect the state of mental health of the woman; given the complexity of the evaluation, the use of psychometric or psychodiagnostic tools for further study is desirable. At the end of the diagnostic procedure, the certificate should include: general information about the patient, any personal and / or family history positive for psychiatric pathology, diagnostic orientation and any psychopharmacological treatments assumed or prescribed. If the conditions envisaged by the law are set, the following wording should be reported: "These conditions are among those provided for by article 6 of law 194/78".
Since this is a service that could conflict with one's own conscience or clinical conviction, the doctor can refuse his own work when you raise conscientious objection, unless this behavior is of serious and immediate harm to the health of the assisted person and must provide the citizen any useful information and clarification (Article 9 law 194/78; Article 22 CDM). Furthermore, the position of "objector" does not relieve the doctor from the obligation to provide the necessary assistance to the woman in the phases preceding and following the interruption.

• Treatment with interferon - The therapeutic use of interferon, currently very limited by the application of the new anti-hepatitis therapeutic protocols, is contraindicated in the case of Mood Disorders. In this case, therefore, the

psychiatric evaluation (and related certification), before starting such therapy and / or during treatment, aims to highlight psychopathological elements and / or significant anamnestic factors that may represent contraindications to treatment .

• Interventions of plastic reconstructive and aesthetic surgery - Psychiatric support interventions both psychotherapic and pharmacological for patients who have to face or who have already undergone post-traumatic reconstructive surgery (eg, in cases of burns), can foresee the issue of a certification. Otherwise, the assessments required before a cosmetic surgery intervention, directly by the patient or, as a preliminary consultation, by the surgeon require, beyond the clinical state, a particular attention to the motivation to change that should be evaluated in the context of the personality of the subject and relationship with one's own body. In this last case it will be opportune to make use of appropriate psycho-diagnostic aids.

• Bariatric surgery - Already the original 1991 NIH guidelines and the totality of the most recent international and national guidelines provide that the obese patient candidate for Bariatric surgery is subjected to a thorough preoperative multidisciplinary evaluation that includes an assessment of mental status. In general, in addition to the clinical interview, a psychometric assessment is useful that includes a personality test, a general psychopathology test and other specific tests that concern eating behavior, body image, quality of life and motivation to change [14].

• Organ transplants - In organ transplantation, destructive or incongruous behaviors have been reported in particularly complex cases; for these reasons it is essential that transplant candidates undergo a careful evaluation, counseling and possible psychological and / or psychiatric assistance. The kidney transplant, for example, while representing the "liberation" from the restrictions imposed by dialysis, often and already in the pre-operative waiting phases, raises doubts, anxieties and possible anguish that in post-transplantation times can become fears for the infections, for the rejection and for the end of a hope with unpredictable results [15]. Transplant patients can therefore develop from simple emotional stress to real affective disorders, such as anxiety and depression with consequent impairment of quality of life [16 17]. The experience of transplantation can also configure a psychosomatic response that requires, in order to be faced and allow the process of adaptation to the "foreign" organ, avoiding possible psychopathological repercussions, the mobilization of all biopsychosocial resources available to the patient [18].

• Prenuptial certificate - The psychiatrist can be requested as an expression of the free will of the couples. In such cases it is first necessary to evaluate the two subjects individually, then, if necessary, integrate the evaluation with appropriate relational techniques in order to deepen the relationship between couples. In any case, it can never have predictive value.

• Certificate of psychophysical suitability for the attainment of the qualification for the use of toxic gases - Doctors of the Hygiene and Prevention Sector, of the Occupational Medicine Service or of the ASL Medical-Legal Office as well as to the military doctors are assigned the competence in the field of certification of psychophysical suitability for the use of toxic gases. These may, therefore, make use of psychiatric counseling to ascertain the absence of mental illnesses and signs of alcohol intoxication or narcotic substances that prevent the safe execution of operations relating to the use of toxic gases (RD 9 January 1927, n. 147 and DPR June 10, 1955, No. 854).

• Certification relating to results of torture and intentional violence - Under the terms of Article 8, paragraph 3-bis, of Legislative Decree 251/2007 (amended by Legislative Decree 142/2015), the Territorial Commission for the recognition of international protection "on the basis of the elements provided by the applicant, may dispose, subject to the applicant's consent , medical examinations aimed at ascertaining the results of persecution or serious damage suffered according to the guidelines referred to in Article 27, paragraph 1-bis, of Legislative Decree 19 November 2007, n. 251, and subsequent amendments. If the Commission does not have a medical examination, the applicant can perform the medical examination at his own expense and submit the results to the Commission for the purpose of examining the application. Certification can help assess the congruence between medical and psychological symptoms and other medical evidence and narrations given by the applicant for international protection regarding torture, ill-treatment or trauma. The certification can also be produced for one or more of the following reasons: 1) to inform about "psychological" difficulties (fear, shame), which the applicant can manifest in the reconstruction of the events, giving indication and explanations on the possible emergence of inconsistencies and contradictions in the narration, due for example to memory disorders or dissociative episodes; 2) to ascertain serious invalidating states or long-term illnesses, which cause fragility and / or the need for long-term and continuous specialized assessments and treatments, as well as, in order to give an indication of the consequences on the mental health of a forced return in the social context, where the applicant has suffered episodes of torture or violence; 3) inform the ascertaining body of the impossibility for the applicant, due to his physical or mental health conditions, to take the hearing; 4) give indications on the opportunity that the applicant, due to the particular condition of emotional fragility or serious psychopathology, is assisted during the audition. The essential condition for being able to draw up a certification related to torture and intentional violence results is, therefore, always represented by a taking charge in a multidisciplinary path, which takes into account the holistic approach to the health and needs of the asylum seeker. The patient / applicant must be evaluated by specially trained personnel within centers recognized by the NHS, whose activity can be monitored and adequately evaluated at all stages of the process.
The doctor who prepares the certification must be impartial and must not express any opinion on the merit of the request for protection. The certification, therefore, should not include conclusions or opinions about the truthfulness

of the applicant's narrative, but should rather limit itself to assessing whether the physical or psychological symptoms encountered are congruent, and to what extent, with the description of the events provided by the applicant with respect to the traumas suffered [19].

• **Certification of mental health** - Considering that the indeterminacy of the demand in the absence of a well-defined purpose can constitute in itself a symptom of a more or less severe mental disorder, it will be necessary to evaluate the awareness of the applicant's illness, any concealments, as well as the its interest in using the certificate for purposes other than those stated. In such cases, prudence requires the most absolute clarity in the information for the purposes of consent, and this primarily through a detailed description of the evaluation procedure, thus communicating to the patient in advance the possibility of finding, at the end of the diagnostic process, of any alterations psychopathological and that, therefore, the content of the certification could report a different evaluation result than expected.

Conclusions

What the doctor is required to declare in the context of certifications, if on the one hand it is limited by respect for the truth, on the other it must always aim at protecting the confidentiality of information and the will of the patient. Faced with these and other problems, the golden rule of medicine assumes even more value for the psychiatrist, for whom systematically operating according to the rules of good practice or in any case of correct action, with diligence, prudence and skill, should represent the cardinal principle on which establish any activity, including certification. It is therefore desirable, on the part of authorities and institutions, to develop national and international guidelines that suggest a unified procedure for drafting the certificate in order to minimize the ambiguity that the psychiatrist is inevitably faced with whenever is called to certify.

Conflict of interests

The authors declare that there is no conflict of interests.

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