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Contents

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Società Italiana di Psichiatria

Letter from SIP Presidents to Minister of Health

Massimo di Giannantonio[1], Enrico Zanalda[2]

[1] Presidente Eletto SIP; [2] Presidente SIP

Massimo di Giannantonio

Enrico Zanalda

The 21st of january 2021 we wrote a letter to Onorevole Roberto Speranza Ministry of Healt. We asked him that as part of the fight against the COVID-19 pandemic our patients be considered with priority for vaccination. The President of the World Psychiatric Association Afzal Javed previously sent a letter to the national psychiatric associations, inviting all members to work towards the protection of people with mental illness during the COVID-19 pandemic.
This was also the message of the WPA's Advisory Committee on Responses to Emergencies (ACRE) at the recent meeting in January. The Committee suggested that Member Societies might wish to approach their respective governments about the need for persons with Severe Mental Illnesses (SMIs) to be considered for priority in vaccination programmes.
Also other several Member Societies like us are already in the process of doing this.
Attached is the content of the letter sent.

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SOCIETÀ ITALIANA DI PSICHIATRIA
Affiliated to World Psychiatric Association

Alla cortese attenzione del Ministro della Salute
On. Roberto Speranza

Durante l'Assemblea Generale che si è svolta nell'ottobre 2020, l'Associazione Psichiatrica Mondiale (World Psychiatric Association, WPA), che rappresenta più di 250.000 psichiatri in 120 paesi, ha adottato una posizione sull'assistenza sanitaria alle persone con malattie mentali durante l'attuale pandemia COVID-19 che ha trasmesso a tutte le società affiliate come quella italiana. Il presidente della WPA, Afzal Javed, ci ha esortato a contattare il Ministero della Salute per sottolineare che le indagini scientifiche hanno dimostrato come le persone con malattie mentali abbiano maggiori probabilità di essere infettate dal COVID-19 e che, una volta colpite, presentino tassi di mortalità più elevati rispetto al resto della popolazione.

Il Comitato Consultivo sulla Risposta alle Emergenze della WPA (Advisory Council on Response to Emergencies, ACRE) di cui facciamo parte come SIP, ha discusso questo problema nella riunione dell'11 gennaio 2021 e si è deciso di rivolgersi alle istituzioni governative e non governative, **per esortarle ad includere le persone con malattie mentali tra i gruppi ai quali verrà data priorità nei programmi di vaccinazione**.

Riteniamo che anche il governo italiano, al pari di altri governi mondiali, debba dare disposizioni in questo senso. L'inclusione delle persone con gravi malattie mentali tra i gruppi considerati prioritari nei programmi di vaccinazione è una decisione da assumere nell'interesse della salute pubblica ed esprime allo stesso tempo il rispetto dei diritti umani delle persone con malattie mentali.

La WPA continuerà a monitorare la situazione nei vari paesi e ad informare gli organismi professionali e governativi sull'impatto della pandemia COVID-19 sulle persone con malattie mentali e le loro famiglie e sugli effetti della vaccinazione contro il COVID-19.

I Presidenti SIP

Prof. Massimo di Giannantonio

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Evidence based Psychiatric Care
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Società Italiana di Psichiatria

Psychiatric expertise: from social control to indication of treatment

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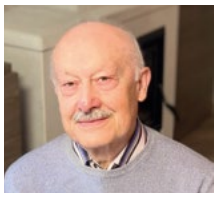
Gian Carlo Nivoli


Mario Amore


Massimo di Giannatonio


Enrico Zanalda

This paper is a psychiatric, clinical and forensic scientific update on psychiatric expertise. It consists of nine forensic psychiatric observations shared and accepted by the Italian Psychiatric Association (SIP) and the Italian Society of Forensic Psychiatry (SIPF), which, according to Italian law (n. 43/2017) have legal value on the subject of good clinical practices and evaluation of the psychiatrist's professional responsibility [1,2].

The contribution of psychiatry to the legal assessment of dangerousness

The concept of dangerousness is a juridical concept on the subject of social defence and social control and is the exclusive competence of the magistrate. It is not the task of psychiatry and forensic psychiatry to assess social defence, social control, establish premeditation, declare aggravating or mitigating circumstances, etc. Psychiatry, in terms of diagnosis and therapy, which is its pertinence and competence, will illustrate to the magistrate the clinical seriousness of the mental disorder and the degree of intensity of the treatment to be applied (on the territory, in the community, in high intensity care facilities such as REMS, etc.), contextualised and feasible in relation to the specific case. The magistrate may use this psychiatric information on the basis of his discretionary power and on the basis of what the law provides for in terms of legal criteria for the assessment of dangerousness.

Sharing between the expert and the case manager

The treatment indications, when appropriate, contained in a psychiatric report (where and by whom the patient must be treated) must be shared between the writer of the report (expert) and the person who will treat the patient (case manager). The shared procedure avoids conflicts of competences between the protagonists of the judicial assessment, dysfunctions in the administration of Justice and Health and is a medical-psychiatric variable that contributes to validate the treatment and rehabilitation paths. The shared information is offered to the magistrate's assessment.

The report as a medical-psychiatric document

The psychiatric report does not only contain the answer to the magistrate's specific questions, but in the information useful for the purposes of justice, it provides a medical-psychiatric documentation useful for the treatment and rehabilitation paths, foreseen by the law, for the patient. This is a medical-psychiatric documentation that will have to follow the patient in his or her therapeutic pathways, which can be easily retrieved by the treating personnel in order to document and validate the treatment choices.

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The difference between Forensic Psychiatry and other neuroscientific disciplines

Aims and methodologies of forensic psychiatry are different from those of other disciplines of knowledge such as clinical psychiatry, psychotherapy, psychology, psychoanalysis, genetics, pharmacotherapy, examination with mental reagents, diagnosis by means of imaging, diagnostic laboratory tests, etc. Confusing the aims and methodology of forensic psychiatry with the aims and methodologies of other disciplines can lead to confusion and errors that reduce the scientific and forensic validity of the report.

Criteria for the forensic validity of an expert report

In order to be declared forensically valid, an expert report must respect some precise criteria. The Italian Psychiatric Association has highlighted a series of variables that must be respected in an expert report: the type of assignment, the diary of the expert operations, the description of the facts for which proceedings are being taken, the medical-psychiatric and possibly criminal anamnesis, the direct psychiatric examination, the clinical evaluation and the causal link, the psychiatric-forensic observations, the answer to the questions. The magistrate, in his capacity as 'guardian of the scientific method', has the right and duty to evaluate the methodology with which the report is drawn up and, if he considers it necessary, to declare it incomplete or even 'inadmissible' at trial.

Appropriateness Criteria of expertise

The psychiatric report, like all medical documentation, must meet the criteria of clinical appropriateness. It must also respect forensic appropriateness and contain all necessary information and not all possible information. The appropriateness of an expert report is based on an accurate clinical and forensic psychiatric assessment of the case, it must be contextualised to the situation for which it was requested.

The qualification of experts

The performance of psychiatric expertise and counselling requires qualification as required by law and by codes of ethics and good clinical care practices. The law in particular requires real expertise on the specific task to be performed. The Italian Psychiatric Association has defined the criteria for the qualification of the psychiatric expert: physician, specialist in psychiatry with at least 8 years of clinical psychiatric care experience in public facilities in addition to the years of specialisation and an adequate curriculum in relation of the case in question. This qualification guarantees the magistrate of the expert's specific competence and ensures that the indications provided are in line with the organisation of the National Health System, which often has to be involved in the subject's treatment pathway.

Recusal and denunciation of expert

The law provides for the objection of experts and advisers when they are not qualified or reliable. There are legal criteria for establishing qualification. There is also specific national case law and a large body of international literature establishing criteria for the reliability of the expert. The request for objection, with adequate reasons, must be submitted to the competent magistrate. The expert and the consultant can be professionally liable for the correctness of their work for any guilty inexperience, negligence and imprudence.

Training and scientific updating in forensic psychiatry

In order to obtain the title of specialist in psychiatry, training in forensic psychiatry and in the assessment of professional responsibility are required by law. These are two specific topics of forensic psychiatry with important consequences in the daily management of psychiatric care. The scientific updating of experts and consultants is a criterion of their qualification and reliability.

Conclusions

The nine forensic psychiatric observations listed above constitute the indispensable premise for the correct execution of a psychiatric expertise. The Magistrate, in the cases provided for by law, may resort to the constitution of a panel of experts. Both the Italian Psychiatric Association and the Italian Society of Forensic Psychiatry consider this modality to be correct if the panel as a whole meets the required qualifications.

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2 Psichiatria forense nella pratica psichiatrica quotidiana. Società Italiana di Psichiatria. Società Italiana di Psichiatria Forense. Introduzione: Di Giannantonio M, Zanalda E, Nivoli G. Scritto presente e liberamente riproducibile dal sito ufficiale della Società Italiana di Psichiatria e della Società Italiana di Psichiatria Forense.

L'expertise psychiatrique: du contrôle social à l'indication aux soins

Société italienne de Psychiatrie, Société Italienne de Psychiatrie Légale

Cet article est une mise à jour scientifique psychiatrique, clinique et médico-légale sur l'expertise psychiatrique pénale. Il s'agit de neuf observations psychiatriques cliniques et médico-légales partagées et acceptées par la Société Italienne de Psychiatrie (SIP) et par la Société Italienne de Psychiatrie Légale (SIPF) qui, conformément à la loi italienne (n 43/2017), ont une valeur juridique en termes de bonnes pratiques cliniques, d'expertise et d'évaluation de la responsabilité professionnelle du psychiatre [1,2].

La contribution de la psychiatrie à l'évaluation juridique de la dangerosité

Le concept de dangerosité est un concept juridique qui concerne la protection sociale et le contrôle social. Il est de pertinence et compétence, selon la loi italienne, exclusivement du juge. La protection sociale, le contrôle social, l'évaluation de la préméditation, des circonstances aggravantes ou atténuantes, etc. ne relèvent pas de la psychiatrie ni de la psychiatrie légale.
Par contre, il est de pertinence et compétence du psychiatre (en termes de diagnostic et de thérapie) de communiquer au magistrat la sévérité clinique du trouble psychique et le type et l'intensité des soins à pratiquer (sur le territoire, dans la communauté, dans des structures dédiées aux patients difficiles tels que residences pour l'execution de misures de surete (REMS), etc.) qui seront adaptées au cas spécifique. Le magistrat pourra utiliser ces informations psychiatriques en fonction de ce que la loi prévoit en termes de critères juridiques d'appréciation de la dangerosité.

L'échange entre qui rédige l'expertise et qui soigne l'expertisé

Les indications au traitement, quand il y en a, sont documentées dans l'expertise psychiatrique (sur laquelle se base, au debut, la prise en charge thérapeutique de l'expertisé) et doivent être partagées entre ceux qui rédigent l'expertise et ceux qui soigneront l'expertisé. Ce partage évite les conflits de compétence entre les acteurs de l'évaluation judiciaire, et aussi les dysfonctionnements administratifs entre les systèmes judiciaire et sanitaire. Il s'agit d'une variable médicale psychiatrique qui permet de documenter et valider les parcours de traitement et de rééducation. Ce partage d'informations psychiatriques est soumis à l'évaluation du magistrat.

L'expertise psychiatrique considérée comme document médico-psychiatrique

L'expertise psychiatrique non seulement contient la réponse aux questions spécifiques du magistrat et des informations utiles aux fins juridiques, mais fournit aussi une documentation médico-psychiatrique utiles aux parcours de traitement et de rééducation de l'expertisé, prévus par la loi italienne. Il s'agit d'une documentation médico-psychiatrique qui est censées suivre l'expertisé dans son parcours thérapeutique et qui doit être facilement accessible aux soignants afin de documenter et valider les choix thérapeutiques nécessaires.

La différence entre la psychiatrie légale et les autres disciplines de la connaissance scientifique

La psychiatrie légale a des objectifs et des méthodologies différents des objectifs et des méthodologies des autres disciplines de la connaissance, telles que : la psychiatrie clinique, les psychothérapies, la psychologie, la psychanalyse, la génétique, la pharmacothérapie, l'imagerie cérébrale avec injection, tests de laboratoire, etc. Melanger les objectifs et la méthodologie de la psychiatrie légale avec les objectifs et les méthodologies d'autres disciplines peut induire la confusion et l'erreur et réduire la validité scientifique et médico-légale de l'expertise psychiatrique.
Les critères de validité médico-légale d'une expertise psychiatrique.
Une expertise, afin d'être considérée valide au niveau médico-légal, doit respecter des critères précis. La Société Italienne de Psychiatrie et la Société Italienne de Psychiatrie Légale a établi un certain nombre de caractéristiques à respecter: le type de mission, le journal des démarches faites par l'expert au cours de l'expertise, la description des faits en question, les antécédents médicaux, psychiatriques et éventuellement criminels, l'évaluation psychiatrique, l'évaluation clinique et le lien médico-légal de causalité entre la trouble psichiche et le comportement criminel, les observations psychiatriques médico-légales, la réponse aux questions. Le magistrat en tant que «garant de la méthode scientifique» a le droit et le devoir d'évaluer la méthodologie avec laquelle l'expertise est rédigée. Le magistrat peut juger l'expertise incomplète ou même «non recevable» au procès à cause de la "non-conformité" à la méthode scientifique et médico-légal.

Les critères de pertinence de l'expertise

L'expertise psychiatrique doit respecter les critères liés à la pertinence clinique comme tous documents médicaux, mais aussi les critères liés à la pertinence médico-légale et contenir toutes les informations nécessaires et non toutes les informations possibles. La pertinence d'une expertise se base sur une évaluation clinique et médico-légale précise du cas, en le contextualisant à la situation specifique pour laquelle elle a été demandée.
La qualification des experts.
L'expertise psychiatrique nécessite une qualification des experts qui la rédigent qui est requise par la loi, au sujet des codes éthiques et des bonnes pratiques de soins cliniques. La loi exige en particulier une réelle compétence sur la tâche spécifique à accomplir. La Société Italienne de Psychiatrie et la Société Italienne de Psychiatrie Légale ont défini les critères de qualification de l'expert psychiatre: il doit être médecin, spécialiste en psychiatrie avec une expérience d'assistance clinique dans une structure publique depuis au moins 8 ans (mise à part les années d'internat) et doit avoir un curriculum professionnel adéquat par rapport à l'évaluation du cas spécifique. Cette qualification garantit au magistrat la compétence spécifique de l'expert pour fournir des réponses aux questions judiciaires et aux questions propres à l'organisation du système national de santé, qui doit souvent être impliqué dans le parcours de soins du patient.

La récusation de l'expert

La loi prévoit la récusation de l'expert (et/ou du consultant) *lorsqu'il n'est pas assez qualifié ou fiable. Des critères juridiques sont requis pour déterminer la qualification. Il existe aussi une jurisprudence nationale spécifique et une large littérature internationale qui établit les critères de fiabilité de l'expert* [1,2]*. La demande de récusation, dûment motivée, doit être transmise au magistrat concerné. L'expert et qui donne un avis psichiatrique judiciaire doivent rendre compte, selon la loi, de l'exactitude de leur travail et de toute éventuelle négligence, imprudence et manque de méthodologie et de connaissance professionelle requise.*
Formation et mise à jour scientifique en psychiatrie légale.
La loi italienne prévoit une formation dans le domaine de l'expertise et dans le domaine de l'évaluation de la responsabilité professionnelle afin d'obtenir le titre de spécialiste en psychiatrie. Il s'agit de deux domaines spécifiques de la psychiatrie légale qui ont des conséquences importantes dans la gestion quotidienne des soins psychiatriques. La mise à jour scientifique des experts fait partie des critères déterminant leur qualification et leur fiabilité.

Conclusions

Les neuf observations psychiatriques médico-légales énoncées ci-dessus constituent la base pour garantir la bonne exécution d'une expertise psychiatrique. Le magistrat, dans les cas prévus par la loi, peut recourir à la création d'un collège d'experts. La Société italienne de Psychiatrie et la Société Italienne de Psychiatrie Légale considèrent que cette méthode est correcte à condition que le collège dans son ensemble satisfasse à la qualification requise.

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Società Italiana di Psichiatria

Compliance, cognition and comorbidity in bipolar disorder

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Mrugesh Vaishnav

Summary

Background: Bipolar disorder (BD) causes unusual shifts in mood and energy levels which can have life-long adverse effects on the patient's mental and physical health.

Aim: To identify and address the unmet clinical needs in diagnostic assessment and therapeutic intervention on compliance, cognitive impairment, comorbid substance use and obsessive compulsive disorder in BD among Indian clinical practice.

Method: A total of eighty-five expert psychiatrists reviewed specific areas of uncertainty and formulate the consensus pertaining to bipolar disorder through focused group discussion sessions (FGDs) conducted across seven cities in India. Themes were used to generate research questions which were thoroughly discussed with the psychiatrists.

Results: Bipolar disorder identification of at-risk populations has been difficult. According to psychiatrists, mania is diagnostic of BD. When patients present with alarming symptoms, psychiatrists consider the condition as BD and were of the opinion that patients should be fully well-versed with manic and depressive symptoms. Further BD has exhibited high rates of treatment non-adherence and in clinical practice psychiatrists observed that personality of patient, medication dose, influence of patient's family member, and stigma are the key factors influencing treatment adherence. Psychiatrists opined that assessment of cognitive impairment is needed during follow-up to plan personalized cognitive remediation in case of definite cognitive deficiency.

Conclusion: In conclusion, BD is a major public health problem complicated by high comorbidity and poor health outcomes leading to significant mortality risk. Patients and family care givers awareness about disease burden, diagnosis and management can reduce complications and enhance outcomes.

Key words: bipolar disorder, compliance, cognition, substance use, obsessive compulsive disorder

Introduction

Bipolar disorder (BD), also known as manic-depressive illness, is a brain disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. The four basic types of BD are: Bipolar I, Bipolar II, Cyclothymia, other specified and unspecified bipolar disorder [1]. BD typically begins in adolescence or early adulthood and can have life-long adverse effects on the patient's mental and physical health,

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Conflict of interest
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educational and occupational functioning, and interpersonal relationships [2].

The prevalence of BD across the world varies from 0.4 to 1.5 percent by country. Globally, an estimated 40 million people in the world had bipolar disorder in 2016, with 0.55 and 0.65 percent being male and female, respectively [3]. According to the 2015-2016 report of the National Mental Health Survey (NMHS), the current and lifetime prevalence of mood disorders including bipolar and depressive disorder in India is 2.84% (95% CI: 2.81-2.87) and 5.61% (95% CI: 5.57-5.65) respectively, while that of BD alone (including single mania and hypomania episodes) is 0.30% (95% CI: 0.29-0.31) and 0.50% (95% CI: 0.49-0.51) respectively [4].

Literature reports that patients with BD often present with depression, mixed state (i.e., depressed mood combined with increased energy, restlessness and racing thoughts), psychosis, manic or hypomanic episodes with rapid cycling between such episodes [5]. Studies report that 50% or more of patients initially present with depression and since MDD and BD have similar symptoms it is very common for BD to be misdiagnosed as MDD [6]. One study reported that over 60% of patients who were eventually diagnosed with BD had previously been misdiagnosed with MDD [7]. Further, patients vary greatly in severity of symptoms and duration of episodes. As a result of diverse symptoms and misdiagnosis, the condition remains unrecognized in many patients for several years often leading to delay in diagnosis.

Even with a successful diagnosis, management of BD is challenging due to wide range of phenotypic expressions and responses to treatment. Although the number of treatments has increased, full recovery is rarely observed as substantial proportion of patients do not respond adequately to drug monotherapy, and combinations of drugs are often required to achieve stability and reduce relapses [8]. In addition to pharmacotherapy, adjunctive psychosocial interventions are also considered in order to improve social functioning, reduce the need for- pharmacotherapy, number of hospitalization and relapse rates [9-12]. Given the demographic, geographical and cultural diversity in India, it becomes essential to understand principles and practice of managing BD among Indian population. Therefore, the objective of the expert consensus document was to identify and address the unmet clinical needs in diagnostic assessment and therapeutic intervention on compliance, cognitive impairment and comorbid substance use and obsessive compulsive disorder (OCD) in bipolar disorder among Indian clinical practice through detailed focus group discussions, involving experts in bipolar disorder so as to aid clinical decision making for practitioners in the complex decision-making process.

Method

An expert panel groups were constituted comprising 85 leading psychiatrists' experts in India who thoroughly reviewed the up to date literature and developed the consensus document.

Results

General considerations

This clinical scientific statement represents the consensus of panel experts who focused on to understand the unmet need and challenges faced during the treatment of BD.

Uncertainties & unmet needs in bipolar disorder

For psychiatric disorders in general, and for BD in particular, identification of at-risk populations has been difficult as there is considerable uncertainty about how to identify high-risk groups and no effective preventive measures are available [8]. The most promising approach so far observed is to follow up children and adolescents who have parents with bipolar disorders [13,14]. To identify at-risk BD population, expert panel were of opinion that mania is diagnostic of BD and when patients present with alarming symptoms they consider the condition as BD and were of the opinion that patients should be fully well-versed with manic and depressive symptoms. Further, expert panel were of the opinion that every patient followed a set pattern of individualized symptoms such as BD episodes and relapse. Moreover, BD has genetic inheritance and runs in the families and thus genetic loading and predisposition is quite high. Behavioral disorder, childhood depression, personality disorder with substance abuse should be screened in patients suspected with BD. ADHD is associated with small children who struggle to pay proper attention in school due to high stress level. Attention deficit is present during inter episodal phase i.e., euthymic phase and thus it should be noted that the symptoms of ADHD often carry on into adulthood merging with symptoms typically associated with adults with bipolar spectrum disorder. Since bipolar is a progressive condition, no specific brain imaging biomarkers are available for identification of at risk population and thus it remains a grey area. However, the clinical benefit of identifying at-risk population needs to be seen.

Further, expert panel were of opinion that diagnosing BD, compliance, polytherapy, patient insight and cultural beliefs are few challenges encountered by them. Compliance is an issue as it takes seven days' time for a medication to work making patients poorly adhere to the treatment. Diagnosing BD particularly misdiagnosis is a challenge. BD is sometimes misdiagnosed as schizophrenia and patients are put on long term antipsychotics which later cause depression in patients. This depression is again seen as negative symptom of schizophrenia and psychiatrist prescribe another medication to treat it ultimately leaving patients with no improvement at all. Thus, it is important to diagnose mania. Also, longitudinal and family history becomes important to diagnose BD. Along with patient's less

knowledge, convincing patient's caregivers/parents is also a practical challenge.
Early intervention aiming to stop or delay the course of BD is appealing. Expert panel opined that diagnosing and initiating BD intervention early results in fewer relapse rate and overall better clinical prognosis of BD which is in line with the published literature. Opinion from expert panel is as mentioned in below box.

Recommendations for unmet need

- Start treatment with low dose and continuous monitoring. In case where patient's RFT is normal, clinical dose must be according to the patient's weight
- Monotherapy is advisable as polypharmacy leads to subclinical dose treatment
- In case of normal SGPT and creatinine levels sodium valproate at a dose of 20 mg/kg should be administered
- Lithium as nutritional supplement in small doses is being used for the prevention of dementia
- Maintenance treatment with lithium monotherapy was superior to quetiapine for clinical secondary outcome measures of depression, quality of life, work functioning
- The depressive phase of bipolar disorder is associated with suicide attempts and unsuccessful treatment of bipolar depression can cause unnecessary suffering and morbidity like substance abuse
- Quetiapine recommended in bipolar type I and type II depression
- Lurasidone recommended in bipolar type I depression
- Lamotrigine alone recommended in bipolar type II depression, while lamotrigine in combination with lithium recommended in bipolar type I depression

Expert panel opined that bipolar disorders are leading causes of disability in young people as they can lead to cognitive and functional impairment and increased mortality, particularly from suicide and cardiovascular disease.
Further, patients with first-episode of BD present with increased psychosocial function compared with patients with multiple episodes [15]. Expert panel were in favor about the combined clinical and psychosocial interventions on symptomatic and functional recovery, including cognitive functioning. They opined that in acute phase mania and depression, psycho education and psychosocial intervention is very helpful. Expert panel were of opinion that delay of correct diagnosis impacts clinical practice. They opined that in most cases when symptoms are observed, parents or family members do not take it seriously and do not come for regular follow-ups. However, when there are severe manic episodes family members considers the seriousness of the condition. Diagnosis delay is particularly observed with younger age of onset. Expert panel were of the opinion that substance use is one of the comorbidity in BD in younger age group. Younger age patients via surfing internet usually concludes what they are suffering from i.e., they have social anxiety or low mood and treat themselves using cannabis where monitoring dose becomes difficult.

Compliance in bipolar disorder

Treatment adherence is an important factor for managing patients with BD in order to prevent relapses, hospitalizations, and other negative consequences. However, BD is expected to be characterized by high rates of treatment non-adherence [16]. Available evidence suggests that 20-60% of the patients with BD become non-compliant with medication and drop out of treatment [17].
Table I enlists determinants of medication non-adherence in BD [16,18]. In addition to these determinants, in clinical practice expert panel have observed that personality of patient, medication dose, influence of patient's family member or relative, and stigma are the key factors influencing treatment adherence. If the patient presents with a break-through episode, the initial strategy is to check the medication compliance and ensure adequate compliance. If compliance is not an issue, initial strategy is to optimize the mood stabilizer which the patient is already getting.

Recommendations for compliance

- Simple dose regimen increase compliance
- Administration of single dose regimen than multiple dose to increase compliance.
- Psychoeducation is the most important parameter to improve compliance.
- Small size of the tablet preferred for long term compliance
- To reduce misconception, explain the cycle of mania and depression to patients and family
- CBT - 8 to 10 sessions required to improve compliance
- Explain patient about importance of medication with examples

Strategies that have been adopted to improve medication adherence include pharmacological and psychological. Adherence in BD often is difficult when patients require a complex medication regimen to control their illness. Literature reports that patients and clinicians may prefer to use once-daily dosing drug formulations, which can pro-

Table I. Determinants of medication non-adherence in BD.

Factors determining medication non-adherence	
Demographic factors	Age, gender, race, education level
Clinical factors	Duration and severity of illness, BD subtype, comorbidity
Treatment related factors	Duration and intensity of treatment, medication side effects
Clinician related factors	Influence of clinician-patient interactions
System related factors	Health system barriers to gaining access to appropriate care
Patient centered factors	Attitudes and beliefs regarding medications, knowledge about the illness and its treatment, role of family members, patient satisfaction

vide consistent serum levels and fewer adverse effects e.g., divalproex extended-release (ER) which showed that 62% patients preferred divalproex ER who were switched from divalproex delayed-release [19]. This is in line with the expert's opinion to use single dose regimen than multiple dose to increase compliance. Similarly, long-acting injectable formulations (LAIs) may be used as maintenance treatment if nonadherence is an issue e.g., risperidone-FDA approved for maintenance treatment of BD-I [20]. However, according to Expert panel, LAIs can be given to prevent relapse of BD. Moreover, if one drug is continuously administered it may create insight in illness, which may lead patient to consume mood stabilizers improving compliance. Thus, with LAIs compliance is increased however further literature search is needed.

Psychosocial strategies such as individual and family psychoeducation, cognitive behavioral therapy (CBT), interpersonal and social rhythm therapy (IPSRT), and family focused therapy are used in BD. Expert panel were of opinion that psychoeducation is the most important parameter to improve compliance apart from medication. Furthermore, tablet-related characteristics such as difficulty in swallowing tablets due to shape and size is one well-known problem among patients which negatively affects their treatment acceptance and preference. Data indicate that less than a quarter of people who have difficulty swallowing their pills discuss the problem with a health professional [21]. To this point Expert panel agreed that the size of the tablet plays a vital role in improving the long-term adherence in BD patients.

However, according to the Expert panel usually adherence to treatment is seen when patients follow-up regularly and based on their symptoms checked. According to Expert panel treatment adherence scales are time consuming and hence not preferred by them. Moreover, they were of opinion that a structured group (including patients and their care givers) is more beneficial than individual CBT.

Cognitive impairment in bipolar disorder

Cognition refers to thinking skills which includes mental processing speed, attention, learning and memory, and executive skills- known as cognitive domains. Problems in lower cognitive domain such as mental processing speed will impair higher cognitive domains such as attention and executive skills. Cognition is impaired during both mania and depression [22]. Expert group opined that during a Depressive episode, people often experience problems related to paying attention, concentrating, remembering things and solving problems, and during a Manic episode cognition is also affected thoughts may be racing and often change content, while the abilities to judge a situation, pay attention and inhibit impulses are limited.

Several investigative techniques are available for diagnosing cognition in BD such as neuropsychological assessment, laboratory assessment, structural neuroimaging and functional neuroimaging. Cognitive functions can be assessed by asking certain questions to patients pertaining to their cognitive problems in daily life. However, it has been observed that in many cases neurological screening is required as patients with cognitive impairment fails to accurately self-report their impairments [22]. Further, Expert panel opined that assessment of cognitive impairment is needed during follow-up to plan personalized cognitive remediation in case of definite cognitive deficiency. There are several cognitive screening tools available such as DSST (Digital Symbol Substation Test), Screen for Cognitive Impairment in Psychiatry (SCIP) and Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) which are of limited use in clinical practice. Several lifestyle factors such as poor sleep and diet, physical inactivity, medical illness, consumption of alcohol and recreational drugs and stress have negative impact on cognition and play a key role in identifying and addressing ways to improve cognition in BD patients [22].

Drugs have dopaminergic & glutamate mechanism will have better for cognition impairment in bipolar disorder. Different drugs with potential beneficial effects for the treatment of neurocognitive impairment have been examined such as mifepristone, lamotrigine, lithium and divalproex, venlafaxine and olanzapine. The following are the opinions from the expert group for different drugs: mifepristone (helpful in visual memory not in executive function); galantamine (helpful in verbal only not in executive function); donepezil (not preferred molecule for cognitive impairment treatment and is not used much in clinical practice); vortioxetine (may be used in mood disorder); modafinil (used in clinical practice, but not much experience in terms of its clinical improvement, and often the improvement in attendance is sustaining); lurasidone & pramipexole (have less effect on cognition impairment); and neuroprotective agents (seems promising, but need more substantial data for their usage in clinical practice).

Of all these, according to expert panel clinically mifepristone and lamotrigine have been the best medication as they improve working memory and have cognitive enhancing effects. Further, expert panel believed that lithium and divalproex are also good drugs however; lithium in higher dose can lead to cognitive impairment. Similarly, carbamazepine also exerts difficulty in remembering short and long-term memory in higher dose. According to expert panel' venlafaxine may improve attention; however, nowadays, it is hardly being used in BD. However, there are different strategies used to prevent cognitive impairment

Recommendations for cognitive impairment

- Clinically mifepristone and lamotrigine have been the best medication as they improve working memory and have cognitive enhancing effects
- Limited use of scales such as SCIP and COBRA for screening cognitive impairment in BD patients in clinical practice
- Implementing functional and remediation techniques for better promising results along with pharmacological treatments

such as memory exercise, no multiple activities at time (only need to focus on one activity at a time), omit drugs which can cause cognition impairment, yoga and mindfulness therapy, identification of comorbidity, gamification for 20 minutes to 1 hour to improves cognition, mobile games may improve cognition and cognition enhancing drug.

In addition to pharmacological treatments, psychological treatments also play an integral part for treating cognitive impairment. Functional remediation and cognitive remediation are two remediation techniques used popularly and have shown promising results. Expert panel believed that remediation techniques help in memory exercise and stimulating brain. Expert panel opined that noninvasive brain stimulation techniques such as transcranial magnetic stimulation (TMS), deep transcranial magnetic stimulation (DTMS) and transcranial direct current stimulation (tDCS) have been neglected in the studies and were in the favor of using them. Further, according to Expert panel repetitive TMS has shown few side effects in BD patients however, it is very much useful in patients with resistant depression. Also, when rTMS is used with mood stabilizers it acts as a temporary cognitive enhancing agent.

Expert panel opines that the clinical benefit of mindfulness based cognitive therapy (MBCT), particularly through increasing the ability to maintain focus over longer periods of time, in cognitive impairment is not clear and needs further research. Further, psychiatrist believe that along with medication, physical exercise, adequate rest, avoiding concomitant medications that interfere with cognitive function, and promoting healthy habits helps managing cognitive impairment in BD patients.

Substance use disorder in bipolar disorder

Lifetime prevalence of substance use disorders (SUDs) is higher in BD than in any other psychiatric disorder, including unipolar depression. Prevalence rate of SUDs in literature ranges from 20%- 70% in patients with BD and contribute to high rates of disability, morbidity, and treatment non-adherence [23]. Various types of SUDs associated with BD includes alcohol, cannabis, tobacco, opioids and benzodiazepines. Across few studies reviewed, alcohol use is associated with a prevalence rate of 42%, cannabis 20%, and other illicit drug associated with a prevalence rate of 17% [24]. According to Expert panel, clinically around 30-60% of SUD is observed in BD patients in India and it depends on the type of substance used. Also rates of SUD ranges from 14% to 65% in inpatient and outpatient treatment setting among Indian patients. The Expert panel observed that excessive cannabis use was associated with an earlier onset of BD after adjusting for possible confounders while excessive alcohol users had a later onset of BD. Further, panel opined that if patient experiences mania he may start drinking beer for alerting his mind. Expert panel believe that BD and substance abuse is bidirectional, sometimes it may be that substance itself may precipitate BD symptom or because of bipolarity, substance use increases.

The expert panel opined that BD in SUD exhibited significantly poorer performance than BD without SUD in visual memory and conceptual reasoning/set-shifting. Expert panel were of opinion that there is dire need to treat SUD in BD as misuse of substance concurrently with serious mental illness like BD can give manic or depressive episode and opined that both the conditions need to be treated simultaneously. Further, in manic episode, patients have tendency for high risk behaviors, like performing unpredicted sex and sharing of needles while using heroine. Therefore, a normal or depressed person will not do unpredicted sex but under the influence of drugs they may indulge in unpredicted sexual activities, whereas the fact is it's not.

Moreover as reported in literature, comorbid alcohol and substance use can precipitate an episode, increase the frequency of episode, may be associated with rapid cycling affective disorder (RCAD), higher risk for suicide, poor response to treatment, longer time to achieve remission, can influence the choice of medication, and can lead to higher vulnerability for side effects [17].

Pharmacotherapy along with psychological interventions may be helpful in management of comorbidity. The sequential selection of drug for SUD in BD is usually oxcarbazepine in higher doses, valproate and topiramate (given after evaluation of RFT in patient). The number of episodes can be managed by administering the patient with mood stabilizers such as valproate, carbamazepine, withdrawal management, psychoeducation, family involvement and CBT. The stable phase of BD can be managed with the aid of life charts, motivational interviewing, integrated therapy, self-help groups, IPSRT, mood stabilizers and relapse prevention medications. Expert panel were of the opinion that first choice would be lithium followed by sodium valproate (if liver function test is normal) and oxcarbazepine (if liver function test is not normal). Drugs such as naltrexone hydrochloride, acamprosate, citicoline are used in case of alcohol use disorder. The other pharmacological therapy preferred for treatment includes antipsychotics, quetiapine, lurasidone, olanzapine + fluoxetine, active withdrawal drugs such as benzodiazepines, baclofen, carbamazepines, drugs for relapse prevention such as naltrexone, acamporosate and antidepressants. Expert panel opined that fear of the consequences of combining alcohol/illicit substances with mood stabilizers may lead some bipolar patients to be nonadherent to pharmacotherapy.

Recommendations for SUD

- Prevalence of substance use disorder in BD patients depends on the type of substance used
- Same diagnostic criteria must be developed for BD and SUD
- Both SUD and BD should be treated simultaneously
- First choice of drug is lithium followed by sodium valproate and oxcarbazepine

Obsessive compulsive disorder in bipolar disorder

Obsessive-compulsive disorder (OCD) is one of the most frequently associated comorbidities in bipolar disorder. The real challenge lies in managing patients with BD-OCD because both mood stabilizing and management of OCD should go hand in hand. Prevalence of OCD may be masked by the presence of manic or depressive symptoms in BD, impact of OCD in BD disability, quality of life, poor functioning, and higher unemployment, episodic course, rapid cycling, frequent hospitalizations [25]. The panel opined that "stepwise" approach should be used when selecting primary mood-stabilizer treatments as well as when considering concomitant use of pharmacological or psychological treatment. Highest prevalence of OCD in BD is documented in studies of remitted patients.

The first line agents preferred for treatment of OCD-BD are combinations of lithium/divalproex+ risperidone, lithium or divalproex + olanzapine, lithium/divalproex + quetiapine. The second line agents preferred are carbamazepine, ECT, lithium or divalproex/asenapine [25]. Valproate is useful in the treating an SRI intolerant OCD and clozapine-induced OCS. In remitted cases of BD, clinicians will be hesitant to start a SSRI because of high propensity of SSRI to induce mood instability. Mood stabilizer along with olanzapine - SSRI/clomipramine combination is also helpful [25]. Lithium though used in management of OCD, evidence has been not yet established. Psychological interventions have become an integral part of treatment in OCD. Meta analyses of cognitive behavioral therapy (CBT) in OCD have shown it to be effective.

Discussion

Given that BD is a major psychiatric illness and about 0.5% of patients suffer from it in India, there is a need to understand clinical practice pattern of expert panel across India with regards to diagnostic assessment and therapeutic intervention on compliance, cognitive impairment and comorbid substance use disorder in bipolar disorder to meet with unmet clinical needs. The long-term course of bipolar disorder is highly variable, associated with both interindividual variation and heterogeneity between patients [8].

Early intervention in bipolar disorders has not received comparable attention, despite a need for early intervention treatment strategies. Very little attention has been paid to studying the effects of early intervention in patients with either a genetic susceptibility to BD or with attenuated symptoms of this disorder. Further, patients often experience several years of depressive symptoms or full-blown depressive episodes before their first episode of mania or hypomania [26]. Many patients experience a significant delay between the onset of their first symptoms and their diagnosis with bipolar disorder. One study indicated that only 53% of patients were correctly diagnosed with bipolar disorder in the first year, while in the remaining patients it took an average of 7.5 years until a correct diagnosis was made [27]. This delay in diagnosis leads to delay in treatment. It has been observed that delayed treatment initiation is linked with an adverse impact on many clinical variables, including poorer social adjustment, more hospitalizations, increased risk of suicide, increased rates of comorbidities (particularly, substance abuse), forensic complications resulting from committing felonies while unwell, and impairment in age-specific developmental task [28].Therefore early intervention for BD is potentially useful strategy however, it warrants further investigation.

Neurocognitive deficits seem to be present not only in the early course of the illness but also in premorbid stages before illness onset [29]. Although the cognitive impairments found in persons with BD are often subtle, improving neuropsychological processing may dramatically improve psychosocial functioning in these patients. It would seem beneficial to consider neuropsychological functioning when developing long-term care plans for individuals with bipolar disorder [30].

Effect of SUDs on bipolar disorder is substantial with a negative impact on symptom presentation, manifestations, course, and treatment adherence and thus SUD and BD need to be treated concurrently.

In conclusion, BD is a major public health problem complicated by high comorbidity and poor health outcomes leading to significant mortality risk, thereby making the primary care physicians and psychiatrist's role vital in improving quality of life. Early recognition and treatment improves outcome. A number of pharmacological treatments such as mood stabilizers, antidepressants, antipsychotics and non-pharmacological treatments such psychotherapy and psycho education are available as acute and maintenance treatments, with the idea of achieving reduced symptoms and enhanced functioning in BD patients. Awareness of patients and family caregivers about disease burden, diagnostic issues, manage ment choices, treatment non-adherence and effectiveness of early intervention can reduce complications and enhance outcomes in substantial proportion of patients.

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Appendix 1. Research Questions Discussed During Focus Group Sessions

Uncertainties & unmet needs in bipolar disorder
How do we improve identification of at-risk bipolar disorder populations?
What are the clinical benefits of early intervention?
What are the effects of combined clinical and psychosocial interventions on symptomatic and functional recovery, including cognitive functioning?
Do you feel that delay of correct diagnosis impact clinical practice?
Is delay in diagnosis a particular problem in patients with younger age of onset?
Digital Platforms for BPD?
Compliance
What are the brief interventions which can increase treatment adherence?
Cognitive impairment in bipolar disorder
In your clinical practice, how do you diagnose the patients with cognitive impairment in bipolar disorder (BD)?
What are the factors influencing cognitive function?
In your clinical practice, how do you manage patients with cognitive impairment in bipolar disorder?
How does medication affect patient's cognition?
Different ways to overcome cognitive difficulties
What are the promising pharmacological treatments?
What are the promising psychological treatments?
What are the non-pharmacological treatments?
What can be other approaches to prevent cognitive impairment in bipolar disorder?
Substance use disorder (SUD) in bipolar disorder
Is there any clinical significance of substance use disorder in bipolar disorder?
Do you feel there is a need to treat substance use disorder in bipolar disorder patients?
In your clinical practice, what are the diagnostic criteria that you follow to identify patients with substance use disorder in bipolar disorder?
In your clinical practice, how do you manage patients with substance use disorder in bipolar disorder?
What do you believe are the medications which can treat different aspects of the treatment process?

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Performance evaluation in the Departments of Mental Health: the implementation of a multidimensional directional dashboard in the Department of the Bari Local Health Authority

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Summary

Background. Performance management is a central topic for the health care sector, not just at the corporate level but also for each organizational unit. Clinical directorates, healthcare districts, and clinical units must develop performance management systems and tools based on their peculiar needs of data and information to support middle managers' decisions and orient clinicians' behaviors. Mental Health is a sector characterized by a series of peculiarities that make it unique compared to other medical disciplines. Also, in this sector, there are some literature attempts to build performance management tools able to help overcome specific critical issues and encourage the continuous creation of value. This research aims to implement in the Departments of Mental Health (DMHs) a multidimensional dashboard for performance evaluation.

Methods. We considered a complete recent dashboard, present in the literature since 2016, whose implementation is still not proved. We discussed and analyzed the dashboard implementation within a working group. We implemented the dashboard on the company intranet. We tested it in last quarter of 2019.

Results. In 12 months, the dashboard has been adapted and contextualized to the DMH of Bari in Italy and data collection has been carried out. The implementation of the dashboard was straightforward and the tool was very versatile.

Conclusions. The implementation of the tool in the Italian DMHs could encourage benchmarking techniques that aim to highlight the effectiveness of high-level strategies to encourage the implementation of virtuous procedures for the continuous creation of value.

Key words: performance management, multidimensional dashboard, Department of mental health, performance indicators.

Introduction

The topic of performance measurement today has also become central for healthcare companies. In fact, at a time characterized by a lack of resources in the face of growing needs, it becomes essential to apply management

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tools and principles that allow to increase quality, reduce costs, make fewer mistakes [1] and focus on continuous value creation. In this perspective, the tools of Performance Management (PM) become fundamental. The PM is understood as a continuous process of identification, measurement, and development of the performance of individuals and groups and the alignment of such performance with the strategic objectives of the organization [2]. At the basis of the PM is the concept of measurement, closely interconnected with the concept of knowledge of complex transformation processes, at the basis of the use of the resources themselves. The measurement of what is done allows organizations [3] to have a direct perception of what is problematic in their performance, to activate change, and to reduce the tendency to satisficing [4,5]. Mental Health, like other medical disciplines, has made attempts to apply the tools of the PM, albeit in a leopard's eye, not overcoming some critical issues that characterize its managerial aspect [6]. Mental Health, in fact, compared to all other medical disciplines, represents a series of peculiarities.

1. It was one of the first sectors of the Italian National Health Service (NHS) that had the courage to start a real process of deinstitutionalization. In fact, it has shifted the focus of assistance from acute hospital units to territorial services [7]. This shift has become a symbol of professional prestige for Mental Health.
2. It has been able to build a chain of services with differential specialist intensity, characterized by a varied mix of clinic, rehabilitation, social inclusion. This organization has been able to reconstruct distinct care settings, which represent natural steps of a possible path for patients [8].
3. It has been able to build a network of relevant relationships for integrated care and rehabilitation paths with other actors of the welfare system [9].
4. It has adopted a holistic approach to patients, integrating the clinical dimension with the psychological, social, occupational dimension [10]. Moreover, in line with what was proposed by WHO [11], it is the only medical discipline that has set as a global goal the recovery [12] and the promotion of personal well-being.
5. Finally, Mental Health has always been confronted with the dimension of chronicity and the global and permanent care of the patient [13]. In doing so, it involves a varied skill mix of professionals characterized by doctors, nurses, psychologists, educators, rehabilitators and social workers, trying to build interoperable languages and procedures within the DMH.

These characteristics, which make psychiatry unique, are coupled with several issues:

1. the departmentalization, understood as autonomy from the other parts of the health service, sanctioned by the law 833 establishing the NHS14, has been exasperated as a foundation for the creation of a stronger professional identity;
2. the departmentalization has not gone hand in hand with the essential need for comparison and integration with other sectors of the NHS (i.e., primary care, services for the disabled, for the elderly);
3. the excessively divisionalized culture has led to simple logistical support between related services such as those for pathological addictions and child neuropsychiatry;
4. finally, the DMH, which was the first to deal with chronicity, integration, and articulation of care settings with variable intensity, developmental trajectories of all current health services [15], is almost absent in the shared evolution of services, in the inter-sectoral integration of pathways, in the mutual professional contamination;
5. moreover, the very DMH that first dealt with a holistic approach and professional integration is perceived by other medical disciplines as an isolated and closed environment;
6. all this is indeed corroborated by the difficulty of developing shared metrics and measuring outcomes, understood as a difficulty in the culture of measurement [6].

This fragmentation has contributed to feeding the stigma and has undermined in the long run the establishment of a trustworthy professional identity. Moreover, it has had consequences on the concept of professional responsibility contributing to the heterogeneity of approaches, including management at the level of individual Italian DMH. In this scenario, the measurement of inputs is essential. But it is more important to measure the transformation processes, traditionally considered as a black box. Investigating the processes that take place within this black box, which are the basis of value creation, can be useful to an open comparison between different systems. Making inter-company and interdepartmental metrics explicit and homogeneous can therefore be a great contribution to the professional community and for the Italian DMHs [16]. From this comparison, it will be possible to identify virtuous realities and winning paths [17]. This allows management to use data for a better allocation of resources, to evaluate coverage and demand rates and to identify the best management strategies in an era of scarce resources [18]. This approach requires a standard (i.e., applicable in all the DMHs) and easy-to-use tool that allows the comparison between the performance of the various DMHs. In 2016 Latorre and collaborators [19] proposed, on the basis of a well-defined methodology [20] and literature data, a dashboard of indicators for the evaluation of performance in Italian DMH. The dashboard is multidimensional and is characterized by 33 indicators organized in three areas (Tab. I). The areas are defined as follows: (i) Context Area that defines the external context in which the hypothetical LHA and DMH insist and work, (ii) Core Area that identifies the main activities of the DMH, and (iii) Organizational Capital Area that refers to the organizational resources of the DMH. The tool represents a complete performance evaluation tool, which has been able to transform the gaps into opportunities [19].

Table I. The proposed Dashboard (adapted from Latorre et al., 2016).

		Indicator	Formula	Target
Context				
	Population and environment Mental Health profile			
	1	Suicide incidence	Number of suicides/year/territorial population	ND
	2	Rate of Emergency Service accesses for Psychiatric pathology	Number of Emergency Service accesses for Psychiatric pathology/year/territorial population	ND
	3	Incidence to the services	Number of first visits/year/territorial population	ND
	4	Prevalence to the services	Number of visits /year	ND
	5	Rate of patients in care	Number of patients visited at least once with individual project/year/territorial population	ND
Core				
	Hospital Activity/Territorial activity			
	1	Psychiatric Complexity Index in hospitalization	Average DRG weight/year	ND
	2	Relevancy index of hospitalizations	Number of hospitalizations with medical primary diagnosis/total of hospitalizations	0
	3	In-hospital mortality Rate	Number of deaths /total of hospitalizations/year	0
	4	Physical restraint Rate	Number of restraints/number of hospitalizations per year	0
	5	Index of outpatient clinical activity	Number of outpatient visits per year/ number of patients in care per year	ND
	6	Hospital activity index	Total of hospitalizations/year	ND
	7	Domiciliary clinical activity index	Number of home visits/number of patients in care/year	ND
	Efficiency			
	1	Number of hospitalizations longer than 45 days/total hospitalizations	Number of hospitalizations longer than 45 days/total of hospitalizations	0
	2	Hospital/Territorial services Integration index	Number of protected hospital discharges (with direct activation of territorial services)/total of hospitalizations	1
	3	Number of hospital discharges with booked outpatient visit within two weeks/Total hospital discharges	Number of hospital discharges with booked outpatient visit within two weeks/Total of hospital discharges	1
	Efficacy			
	1	Involuntary Treatment incidence	Number of Involuntary Treatment/total of hospitalizations/year	0
	2	Rehospitalization rate	Number of re-hospitalized patients within 30 days from discharge/total of discharges	0
	3	Patient satisfaction index	Verona Service Satisfaction Scale 20	20
	Safety			
	1	Incidence of accidents at work	Number of accidents/year	0
	2	Incidence of emergency calls	Number of emergency calls (or public forces calls)/ number of patients in care/year	0
	3	Incidence of patients complaints	Number of legal complaints/number of patients in care/ year	0

(continued)

Although this tool has already been present in the literature for some years, no application cases are known to date. Therefore, the real feasibility of its contextualization in a DMH is not known. Our main objective was to plan and implement the application of the dashboard in the DMH of the Bari Local Health Authority.

Materials and methods

The application of the dashboard was carried out in the DMH of the LHA of Bari. Its implementation was endorsed by the general direction of LHA. A preliminary step was the sharing of the need to use the tool with the company's Strategic Management. This determined the inclusion of

Table I *(follows)*. The proposed Dashboard (adapted from Latorre et al., 2016).

		Indicator	Formula	Target
Organizational Capital				
	Human resources			
	1	DMH staff completion index	Number of DMH operators/expected number of operators	1
	2	Equipe completion index	Number of complete equipes/Number of active services	1
	3	MHHU staff completion index	Number of MHHU operators/expected number of operators	1
	Training and innovation			
	1	Innovation index	Number of DMH research projects/average number of LHA Departments projects per year	1
	2	Staff continuous training index	Medium number of formative credits per employee/ Number of formative credits required by law per year	≥ 1
	3	IT index	IT assisted services/total of services	1
	Structural resources			
	1	Bed availability index	Beds available/expected beds	1
	2	Bed need index	Number of extra-LHA emergency hospitalizations/total of hospitalizations	0
	3	Safety index of structural resources	Standards compliant service/Number of services	1

the dashboard implementation process among the exercise objectives assigned by the General Manager for the DMH for the year 2019. The implementation process required the support of the Information Systems Analysis Operating Unit of the LHA.

The DMH of the Bari LHA covers a territory that serves the psychiatric care needs of a population of about 1,300,000 inhabitants. The assistance for acute cases is currently provided by the two Mental Heath Hospital Units (MHHUs) available on the territory. The territorial assistance for adults is organized by seven territorial areas. In each territorial area, there are different service units.

We organized a specific working group, including at least one referent person for each territorial area and MHHU. The working group was composed of 15 operators, including the coordinator of the DMH Board. The group was composed of 5 psychiatrists, four nurses, one social worker, two psychologists, three educators/psychiatric rehabilitation technicians.

Three methodological steps were followed to implement the dashboard:

1. discussion and analysis of the dashboard with the working group and identification of data sources;
2. sharing of the dashboard with the Information Systems Analysis Operating Unit and implementation of a platform usable on the company intranet network;
3. data entry for the second half of 2019.

During the first step, every single indicator of the dashboard has been analyzed in order to evaluate its contextualization and consider its possible modification. For each indicator we identified both the competence of the survey service (MHHU, DMH, or DMH management) and the source of the data (i.e., medical records, regional IT systems - SISM or Edotto). In this step, each operator was also trained to collect the data from the identified source. This phase required the first two months of the year 2019 for a total of 3 meetings of the group. The meetings were all directed by the coordinator of the DMH Board.

The second phase was completed with the support of the Information Systems Analysis Operating Unit that built a data entry form on the company intranet platform. We evaluated as constraints the restricted access to all the project referents and the real-time data entry.

The third step involved each territorial referent who manually filled the data entry form accessing the database on the company intranet.

Results

The discussion of the dashboard with the working group led to considerations regarding: (i) the identification of the services of relevance for the imputation of data for each indicator, (ii) the sources to be used for the data collection, (iii) the contextualization of the indicators (Tab. II).

Because of missing historical data, we consider data extracted by the literature as target values. The targets for next years will be defined using the results of the analysis of the first year, after discussing and evaluating the margins for improvement.

Regarding the data collection intervals, we decided to feed the dashboard every three months. This timing maps the due communication of activity data by the company macrostructures to the Operational Management Control Unit. We also validated this interval considering: (i) the cost of manual data entry by each operator, (ii) the loss of non-structured data, and (iii) the use of the punctual data

Table II. Dashboard discussion results.

		Indicator	Relevant Service	Source
Context				
	Population and environment Mental Health profile			
	1	Suicide incidence	ALL	ISTAT
	2	Rate of Emergency Service accesses for Psychiatric pathology	ALL	Edotto
	3	Incidence to the services	Territorial Service	SISM
	4	Prevalence to the services	Territorial Service	SISM
	5	Rate of patients in care	Territorial Service	SISM
Core				
	Hospital Activity/Territorial activity			
	1	Psychiatric Complexity Index in hospitalization	MHHU	Edotto
	2	Relevancy index of hospitalizations	MHHU	Edotto
	3	In-hospital mortality Rate	MHHU	Medical Records /Edotto
	4	Physical restraint Rate	MHHU	Medical Records
	5	Index of outpatient clinical activity	Territorial Service	SISM
	6	Hospital activity index	MHHU	Edotto
	7	Domiciliary clinical activity index	Territorial Service	SISM
	Efficiency			
	1	Number of hospitalizations longer than 45 days/total hospitalizations	MHHU	Edotto
	2	Hospital/Territorial services Integration index	MHHU	Medical Records
	3	Number of hospital discharges with booked outpatient visit within two weeks/Total hospital discharges	MHHU	Medical Records
	Efficacy			
	1	Involuntary Treatment incidence	Territorial Service	Data according to DGR Puglia 162 2014
	2	Rehospitalization rate	MHHU	Edotto
	3	Patient satisfaction index	MHHU/Territorial Service	VSSS-20 scale
	Safety			
	1	Incidence of accidents at work	MHHU/Territorial Service	Administrative acts
	2	Incidence of emergency calls	Territorial Service	Administrative acts
	3	Incidence of patients complaints	MHHU/Territorial Service	Administrative acts
Organizational Capital				
	Human resources			
	1	DMH staff completion index	MHHU/Territorial Service	DMH management acts
	2	Equipe completion index	Territorial Service	DMH management acts
	3	MHHU staff completion index	MHHU	DMH management acts
	Training and innovation			
	1	Innovation index	Territorial Service/MHHU	DMH management acts
	2	Staff continuous training index	Territorial Service/MHHU	Agenas
	3	IT index	Territorial Service/MHHU	PC verified usage
	Structural resources			
	1	Bed availability index	MHHU	DMH management acts
	2	Bed need index	MHHU	Edotto
	3	Safety index of structural resources	MHHU/Territorial Service	DMH management acts /DVR

for steering decisions to reach the targets.
The second step regarded the implementation of a data entry form, on the company intranet site, for the 33 indicators of the dashboard. Each operator was provided with the access link to the intranet platform page, to be accessed through personal credentials. Each operator is enabled to enter data only for the territorial area to which s/he belongs. Several queries can be accessed in real-time by the referent of DMH Board (e.g., overall data of the Department, data of a critical territorial area) (Fig. 1). The implementation of the system was completed by the end of 2019.
The data collection revealed a series of critical issues limited to a few indicators, which are reported in Table III.
We were able to test the working dashboard for the last quarter of 2019.

Discussion

In this study, we have shown the steps of the implementation of a multidimensional dashboard of performance indicators for Italian DMHs. The methodology for the implementation of the dashboard at the DMH of LHA Bari included 3 steps. A preliminary step was to include the dashboard implementation process among the operational objectives for the year 2019 for the entire DMH. We found this preliminary step necessary to obtain the support of the Strategic Company Management. Thus, the Department's management and its structures were motivated and responsive to achieve the goal. The establishment of a working group, including different professional figures representing all the units, allowed: (i) to discuss and promote the tool at all professional levels, (ii) and to share the responsibility on training and data collection.

SISTEMA AZIENDALE DI RILEVAZIONE DEGLI INDICATORI

LATORRE*VALERIA [Disconnessione

RILEVAZIONE DELLA PERFORMANCE NELL'AMBITO DELLA SALUTE MENTALE

Home Page | Rilevazioni | Parametri | Indicatori | Abilitazioni | Informazioni su ...

PARAMETRI DI RIFERIMENTO

Anno: 2018

Tab. 3 - Cruscotto Finale Indicatori area CONTESTO

Profilo di Salute psichico della popolazione e caratteristiche del contesto

Indicatore	Parametro	Valore
Incidenza di suicidi (ISTAT)	Numero dei suicidi nel Periodo	0
Tasso di ricorsi al P.S. per patologia psichiatrica	Numero di ricorsi al P.S. per patologie psichiatriche nel Periodo	0
Incidenza al servizio	Numero prime visite nel Periodo	0
Prevalenza al servizio	Numero di Visite effettuate nel Periodo	0
Tasso di utenza incarico	Numero Utenti visitati almeno 1 volta con progetto nel Periodo	0

Tab. 4 - Cruscotto Finale Indicatori area CORE

Attività Clinica Ospedaliera/Territoriale

Indicatore	Parametro	Valore
Indice complessità psichiatrica ricovero	Peso medi DRG medio nel Periodo	0
Indice appropriatezza utilizzo SPDC	Numero di ricoveri con diagnosi principale medica in SPDC nel Periodo	0
Tasso di mortalità intraospedaliera	Numero di morti nel Periodo	0
Tasso di contenzione	Numero di contenzioni nel Periodo	0
Indice attività clinica ambulatoriale	Numero di visite nel Periodo	0
Indice attività clinica ospedaliera	Numero di ricoveri totali nel Periodo	0
Tasso di attività clinica domiciliare	Numero interventi domiciliari|Numero utenti in carico nel Periodo	0

Efficienza

Indicatore	Parametro	Valore
N. di ricoveri con degenza superiore ai 45 gg/N. totale di ricoveri	Numero di ricoveri con degenza superiore ai 45 gg nel Periodo	0

Figure 1.
Data Entry Form.

Table III. Indicators with data collection issues.

		Indicator	Issues
Context			
	Population and environment Mental Health profile		
	1	Suicide incidence	Out of date data
	2	Rate of Emergency Service appeals for Psychiatric pathology	Available only in the following semester
Performance			
	Efficacy		
	2	Re-hospitalization rate	It will be obtained by the Region
	3	Patient satisfaction index	Reduced Sample
	Structural resources		
	2	Bed need index	Available in the following semester after the end of the current year

The planning of the actions, the contextualization of all the indicators, and the identification of the sources were essential to induce a change in all operators towards the culture of measurement. The members of the working group have naturally become promoters of this tool with their own colleagues.

The step that required more attention from the technological point of view was to bring the dashboard on a mask that could be shared on the network by the contacts of all areas, both for the input of data and for the comparison of their data with those entered by other territorial areas.

The participation and support of the Information Systems Analysis Operating Unit were fundamental for the implementation to grant the use to a shared database on the company intranet and to guarantee a restricted access to protected official data. This official integration allows the unit operator to perceive this tool as part of standard practice.

The persistence of data on the company intranet will allow us to perform comparative analysis over time. The input of data into the dashboard has been followed punctually. The emerging problems were mainly related to the data concerning the first area of the dashboard: the context area. In fact, ISTAT data on the number of suicides are related to past years. Since the publication of the National Mental Health Report 2018 is currently underway, this indicator could be modified in relation to the number of patients with schizophrenia in the region in the last published report. In fact, it is among the diseases that, according to the latest reports, absorbs most of the resources of public services.

A further criticality was related to the data of hospital emergency rooms because available on a different IT system. This leads to an objective barrier in obtaining quarterly data because some data are available only six months after the end of the year of interest. The implementation of the dashboard at the regional level and the synchronization of the data directly from the Edotto system and SISM could be not only the most desirable solution but also the solution that most could exploit the usefulness of the tool.

The goal of this paper is to present the process of implementation of the dashboard, not yet the performance results, which are not reported as limited to last quarter of 2019.

Although using data retrieved in only one quarter, the dashboard results led the working group to several considerations for improvements in: (i) how to collect the data, (ii) how to enter it into the database, (iii) best practice to be enforced.

We mention just one observation regarding the restraint index in the two MHHUs. This index, obtained from the ratio between the number of restraint events and the number of total hospitalizations in a given period, generated two very different results in the two cases. In fact, one MHHU obtained an index of 0.49 (34 restraint events out of 69 hospitalizations in the last quarter of 2019), the other one obtained an index of 3.39 (271 restraint events out of 80 hospitalizations in the same time frame). This discrepancy led to a comparison with the restraint procedures in the two hospital services. A focus group, led by an operator, found that the MHHU with a lower number of restraints implemented updated forms, thus more careful monitoring of the number of restraints, with the aim of reducing the events [21]. Therefore, the working group proposed to DMH Management, in compliance with the recommendations on the prevention of restraint [22], to work on a common, virtuous procedure for the management and monitoring of restraint events. The target for the year 2020 will be to reduce the index by 50% compared to 2019.

Conclusions

We can conclude that the implementation of the dashboard is fairly easy. However, it requires the essential support of the company's Strategic Management, the direct involvement of all DMH structures, and the technological support of the IT units. The dashboard is easy to contextualize. In most cases data can be obtained from the Mental Health Information System, present in every Italian region.

In other cases, data can be obtained from the administrative records of each service or from monitoring sheets that respond to national recommendations.
Considering all the peculiarities of Mental Health and the heterogeneity of approaches, including the management of Italian DMHs, we advise a wide implementation of the tool to increase the culture of measurement, allowing comparisons not only at an intra-departmental level, but especially at an inter-departmental level. At an intra-departmental level, historical data could be used to improve performance and strengthen internal cohesion. On the other hand, inter-departmental comparison and discussion could highlight the effectiveness of benchmarking techniques and high-level strategies, in order to encourage the implementation of virtuous procedures for continuous value creation. We believe that peer comparison, exploration and measurement of work processes, that characterize what was once perceived as a black box, can in the long run diminish the fragmentation that characterizes Mental Health even compared to other medical disciplines. This can also strengthen professional identity, contribute to the heterogeneity of approaches with important consequences also on professional liability.

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Updates in treating major depressive disorder in the elderly: a systematic review

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Summary

Among mental disorders, late life depression occurs in 7% of the general older population.

An updated systematic review of randomized controlled trials (RCTs) on pharmacological and non-pharmacological treatment of major depressive disorder (MDD) in the elderly was conducted.

Eight RCTs were carried out on 663 patients (mean age 70.99, SD 6.73). Vortioxetine (p = 0.897), saffron (η^2 = 0.008) and tianeptine (p = 0.32) reduced depressive symptoms in MDD older adults, although no significant differences in their efficacy were found when compared to sertraline and escitalopram, respectively. Focusing on adverse events, in comparison with sertraline, vortioxetine did not show any significantly difference, while saffron was associated to less neurological disorders (RR 0.13, 95% CI 0.17-0.93, p = 0.02). Neurological (RR 0.46, 95% CI 0.3-0.71, p = 0.000) and gastrointestinal (RR 0.54, 95% CI 0.31-0.96, p = 0.04) disorders were also less common in patients under tianeptine compared to escitalopram.

Although significant effects for some pharmacological and non-pharmacological interventions in older patients, the overall MDD evidence is still scant and more studies are needed in this vulnerable segment of population.

Key words: elderly, major depressive disorder, treatment

Introduction

The world's population is ageing rapidly. As reported by the World Health Organization (WHO), between 2015 and 2050, the proportion of the world's older adults is estimated to almost double from about 12% to 22% [1]. Older adults make important contributions to society as family members, volunteers and as active participants in the workforce. The protection of the physical and mental health status of this vulnerable segment of population needs to be recognized as a real public health priority [2].

Among mental disorders, late life depression occurs in 7% of the general older population and accounts for 5.7% of Years Lived with Disability (YLDs) among those over 60 years old 1. Diagnosing depression in older adults can be more difficult than in young people because of physical comorbidities and cognitive dysfunction [3,4]. Depressive symptoms are often overlooked and untreated and they are accompanied by poorer functioning compared to chronic medical conditions [5,6]. Moreover, depression can increase the perception of poor health, the utilization of health care services and costs, as well as the burden on their families and caregivers [7].

There is no single preferred intervention for depression in older adults, and a wide variety of treatments can be used [8]. Findings from a systematic re-

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Author contributions
The manuscript has been approved by all authors. Studies were identified and independently reviewed for eligibility by the two authors (Amerio, Aguglia) in a two-step based process. Data were extracted by one author (Amerio) and supervised by a second author (Serafini) using an ad-hoc developed data extraction spreadsheet. Our manuscript has been approved by all authors.

view conducted in 2017 by Krause and colleagues on randomized controlled trials (RCTs) revealed several antidepressants and quetiapine to be efficacious in elderly patients with major depressive disorder (MDD), but due to the comparably few available data, results were not robust [9]. Moreover, although significant effects were found for some non-pharmacological treatments, the overall evidence was insufficient, because of based on a few trials with small sample sizes [10].

Aim of the study

We updated Krause and colleagues' systematic review of all RCTs on pharmacological and non-pharmacological treatment of MDD in the elderly to provide recommendations for clinical management and future research.

Methods

Information sources and search strategy

This systematic review was conducted according to methods recommended by the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11,12]. Studies were identified searching the electronic databases MEDLINE, Embase, PyscInfo, CINAHL, ClinicalTrials.gov, Web of Science, and the Cochrane Library. We combined free text terms and MeSH heading as described in Appendix 1. As done before [13,14], the strategy was first developed in MEDLINE and then adapted for use in the other databases. Studies in English published from December 12th, 2017 to January 1st, 2021 were included. In addition, further studies were retrieved from reference listing of relevant articles and consultation with experts in the field.

Study population and study designs

We searched for RCTs carried out in elderly patients with a primary diagnosis of major depressive disorder. The diagnosis was made according to the Diagnostic and Statistical Manual (DSM) criteria for major depressive disorder, or the International Statistical Classification of Diseases (ICD-10) criteria for recurrent depressive disorder. Studies using other diagnostic criteria were excluded. However, as done previously [9], given the variety of depressive forms, studies were accepted if less than 20% of population had another form of depression. Studies of relapse prevention carried out in non-acute patients were excluded.

Interventions

Pharmacological and non-pharmacological interventions, such as psychotherapy and physical activity, were included. Active controls were allowed as well as placebo. Due to either scarce clinical relevance for the elderly and the risk of confounding factors, we excluded studies of combination therapy.

Outcomes

The number of patients responding to treatment was the main outcome, defined as a score reduction of at least 50% from baseline to endpoint or follow-up on a validated scale. In addition, remission of symptoms was defined as: 7 or less on the 17-item Hamilton Depression Rating Scale (HDRS); 8 or less for longer versions of HDRS; 6 or less on the Montgomery-Asberg-Depression Scale (MADRS); 10 or less on the Beck Depression Inventory (BDI); 5 or less on the Geriatric Depression scale (GDS). The mean reduction of depressive symptoms from baseline to the endpoint was also investigated. Moreover, the incidence and main causes of adverse events were included as outcomes of primary interest, as well as dropouts, deaths, and suicides.

Study selection and data extraction

Identified studies were independently reviewed for eligibility by the two authors (MA, AA) in a two-step process: a first screening was performed based on titles and abstracts, then full texts were retrieved for a second screening. Disagreement was resolved by consensus. Data were extracted using an ad-hoc developed data extraction spreadsheet.

Data items

Information was extracted from each included study on: 1) study design, time and country of intervention, sample size, study arms; 2) age, sex and comorbidities of participants; 3) type, name, dose and duration of interventions and controls; 4) name of rating scales, baseline and completion mean rating scores in study groups, Relative Risks (RRs) of response to treatment and symptom remission; 5) frequencies and descriptions of adverse events and dropouts.

Quality assessment

The revised Cochrane risk of bias tool for randomized trials (RoB 2) was used to assess the risk of bias in individual studies [15].

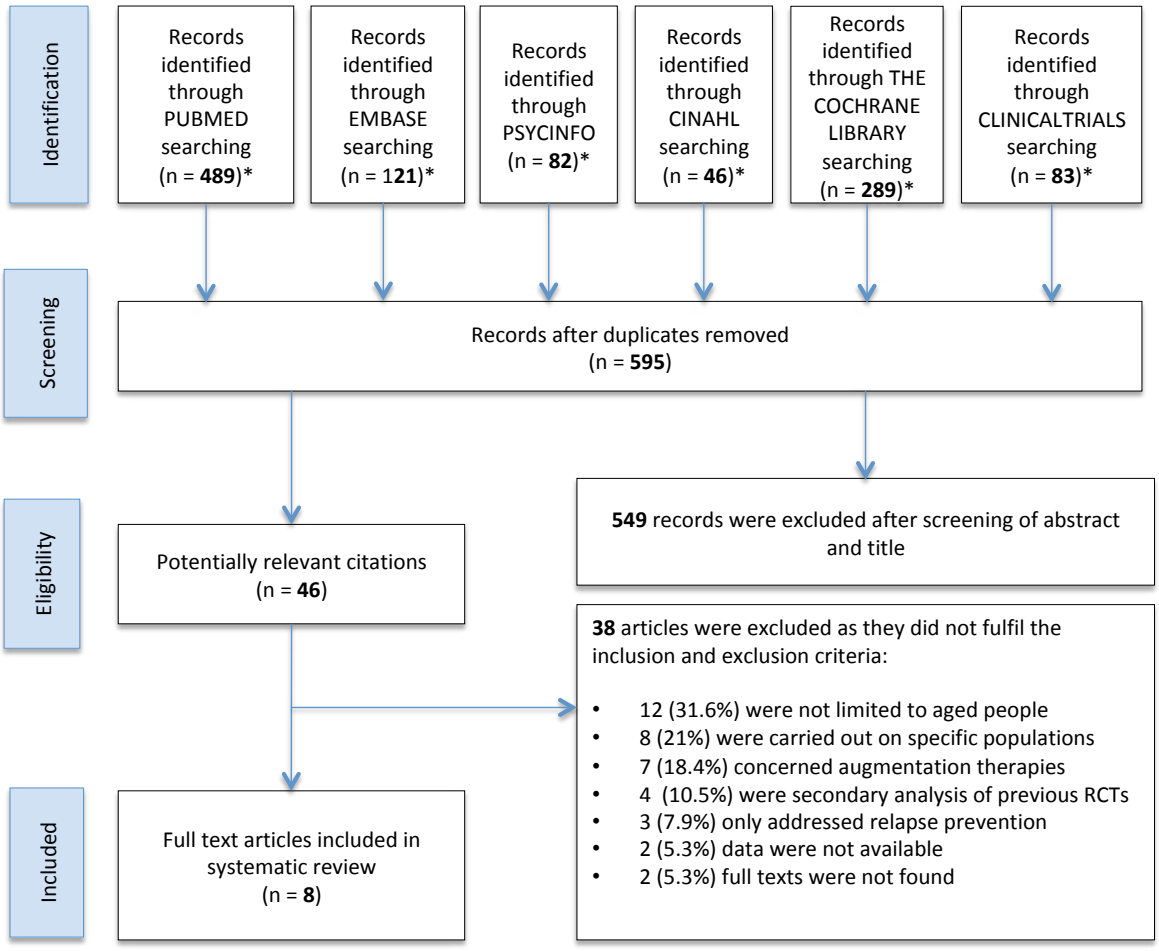
Results

Study selection

Six hundred eighty potential studies were identified from the selected databases and after cross-checking references of relevant articles. Five hundred ninety-five studies were retrieved after duplicate removal. Studies were screened and selected as described in Figure 1. Eight RCTs were included in the systematic review.

Study characteristics and populations

Characteristics of included studies are reported in Table I. All the studies were RCTs and half were double-blind-



** Search strategy limited from December 12th, 2017 to January 1st, 2021, English language, human subjects, aged 65 or more.*

Figure 1. Flow diagram of selected articles.

ed [16-19]. All the trials were two-armed except for one three-armed RCT [18]. The study sample sizes ranged from 20 to 311 patients, with a total sample size of 663.

Three studies (37.5%) were carried out in North America 19-21, two (25%) in the Middle East [16,17], one (12.5%) in Asia [22] and one in Europe [23]. The remaining trial was conducted in different centers of Europe, Asia, and America [18]. The mean age ranged from 68.85 ± 6.16 to 88.3 ± 5.3 [20,23]. The combined mean age of the review was 70.99 ± 6.73.

One trial was entirely carried out on men [23]. The rate of females in the remaining studies ranged from 30% [16] to 74.36% [22]. The overall female rate of the review was 64.71%.

Participants of all studies were included based on an objective diagnosis. DSM-5 was used by three (37.5%) studies [16,17,19], while the fourth edition was used by two (25%) [18,21]. Three studies (37.5%) reported using the Structured Clinical Interview for either DSM-IV or DSM-5 [17,19,21]. One study (12.5%) used the Mini-International Neuropsychiatric Interview (MINI) [22]. The remaining two studies (25%) reported a diagnostic score on respectively the 17-item HDRS [20] and the GDS [23].

Pharmacological interventions

As shown in Table II, pharmacological treatments were studied by four RCTs (50%), accounting for 450 (67.87%) of the overall patients in review. Saffron [16], vortioxetine [17], tianeptine [18], and levomilnacipran [19] were investigated. Sertraline, at mean doses of 100 and 75 mg/die respectively, was used as an active control in two studies [16,17]. One trial was placebo-controlled [19], while another one adopted both placebo and active control with escitalopram 10 mg/die [18]. Interventions were completed after six [16,17], eight [18] or twelve weeks [19].

Non-pharmacological interventions

Four studies (50%) performed non-pharmacological interventions, accounting for about 32.13% out of the review overall sample size [20-23].

Two trials (25%) performed different types of reward-based psychotherapies and multidomain interventions [21,22]. Both trials performed psychotherapy-based controls. One study (12.5%) reported an intervention consisted in a 10-min-

Table I. Study populations and characteristics.

Author	Year	Country	Study Design	Study Arms	Sample Size			Age	Female Rate		Diagnostic criteria	Risk of bias*
					Tot.	Treat.	Ctrl.					
					n	n (%)	n (%)	mean,SD	n	%		
Ahmadpanah et al. [16]	2019	Iran	DB-RCT	2	50	25	25	65.6, 4.32	15	30.00%	DSM-5	Low
Borhannejad et al. [17]	2020	Iran	DB-RCT	2	60	30	30	70.64, 8.26	37	61.67%	SCID (DSM-5)	Low
Emsley et al. [18]	2018	Multi-center	DB-RCT	3	311	105	107 (placebo)	70.44, 4.78	225	72.35%	DSM-IV-TR	Low
							99 (escit.)					
Ionson et al. [20]	2018	Canada	RCT	2	83	40	43	68.85, 6.16	57	68.67%	HRSD-17	High
Krause-Sorio et al. [19]	2019	USA	DB-RCT	2	29	17	12	71.52, 5.79	14	48.28%	SCID (DSM-5)	High
Roh et al. [22]	2019	Korea	RCT	2	78	38	40	74.0, 5.8	58	74.36%	MINI	Low
Solomonov et al. [21]	2020	USA	RCT	2	32	16	16	72.35, 8.12	23	71.88%	SCID (DSM-IV)	Some concerns
Verrusio et al. [23]	2018	Italy	RCT	2	20	10	10	88.3, 5.3	0	0%	GDS	Some concerns

*DB-RCT: Double-Blind Randomized Controlled Trial; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; SCID: Structured Clinical Interview for DSM; HRSD-17: 17-item Hamilton Depression Rating Scale; MINI: Mini-International Neuropsychiatric Interview; GDS: Geriatric Depression Scale. * Summary evaluation according to the revised Cochrane risk of bias tool for randomized controlled trials.*

utes phone call per week and 60-minutes home visits every four weeks [22].
One study (12.5%) carried out one session per week of meditation practices. Sessions lasted 60 minutes. The trial was controlled by treatment as usual consisting in antidepressants and supportive psychotherapy [20].
The last study [23] performed three 45-minutes sessions of physical activity per week, with use of Human Body Posturizers (HBPs) in the treatment group.
Trials were completed after either nine [22], twelve [20] or twenty four [21,23] weeks.

Outcome measurement

Six studies (75%) rated the variations of symptoms with the HDRS, either in its 17-item [16-18,20] or 24-item versions [19,21] (Table III). The last two studies adopted the MADRS [22] and the GDS [23], respectively.

Treatment response, remission and reduction of symptoms

We were able to determine the effect sizes and significance levels for treatment response and symptom remission of four (50%) pharmacological [16-19] and one (12.5%) non-pharmacological interventions [20].
With regard to pharmacological RCTs, the comparisons of saffron [13] and vortioxetine [14] with sertraline were not different for reduction of depressive symptoms ($\eta^2 = 0.008$ and $p = 0.897$, respectively). Symptom reduction was as well no significantly different between tianeptine and escitalopram ($p = 0.32$) [15]. Vortioxetine showed no significant difference with sertraline in treatment response (RR 1.02, 95% CI 0.67-1.55, $p = 1.00$) [17]. Differences in remission probability for saffron (RR 1.0, 95% CI 0.61-1.63, $p = 1$) [16] and vortioxetine (RR 0.6, 95% CI 0.25-1.44, $p = 0.38$) [17] compared to sertraline had a poor statistical significance. Levomilnacipran had no significant effect on remission compared to placebo (RR 1.41, 95% CI 0.31-6.51, $p = 1$) [19].
In one non-pharmacological RCT, meditation practice showed a small effect size and little significance level for response (RR 2.58, 95% CI 1.00-6.67, $p = 0.06$), whereas remission rates were consistently higher in the control group rather than the intervention group (RR 0.24, 95% CI 0.05-0.42, $p = 0.03$) [20].
Multidomain intervention showed a significant reduction of depressive symptoms compared to supportive therapy (score difference: 5.117, $p = 0.029$) [22]. One intervention of reward-based psychotherapy reduced the symptoms as well as problem-solving therapy in control group ($p < 0.0001$) [21]. Physical activity with HBPs significantly contributed to depressive symptom reduction compared to classic physical exercise ($p = 0.01$) [23].

Table II. Characteristics of interventions

Author	Year	Sample Size			Study Duration	Treatment		Control	
		Tot.	Treat.	Ctrl.		Name	Characteristics	Name	Characteristics
		N	N. (%)	N. (%)	Weeks				
2.1. RCTs of pharmacological interventions									
Ahmadpanah et al. [16]	2019	50	25	25	6	Saffron (C. Sativus L.)	60 mg/die	Sertraline	100 mg/die
Borhannejad et al. [17]	2020	60	30	30	6	Vortioxetine	15 mg/die	Sertraline	75 mg/die
Emsley et al. [18]	2018	311	105	107	8	Tianeptine	50 mg/die	Placebo	
				99				Escitalopram	10 mg/die
Krause-Sorio et al. [19]	2019	29	17	12	12	Levomilnacipran	40 (20-120) mg/die	Placebo	NA
2.2. RCTs of non-pharmacological interventions									
Ionson et al. [20]	2018	83	40	43	12	Sahaj Samadi meditation	60 min 1/week	Treatment as usual	antidepressants supportive psychotherapy
Roh et al. [22]	2019	78	38	40	9	"Gold Medal Program" multidomain intervention	10-min phone call: 1/week 60-min visit: 1/month	Supportive therapy	10-min phone call: 1/week 60-min visit: 1/month
Solomonov et al. [21]	2020	32	16	16	24	"Engage" psychotherapy	NA	Problem-solving therapy	NA
Verrusio et al. [23]	2018	20	10	10	24	Physical activity with Human Body Posturizer (HBP)	45 min 3/week	Physical exercise training	45 min 3 sessions/week

NA: Not Available

Dropouts and adverse events

Attrition rates of five (62.5%) studies [16-20] ranged from 11.25% [18] to 51.72% [19] (Table III). The effect size for dropouts due to adverse events in treatment compared to placebo was high in one RCT, with strong inconsistence (RR 5.38, 95% CI 0.66-44.04, p = 0.1) [20].

The effect sizes and significance levels of adverse events were drawn out for the pharmacological interventions [16-19] (Table IV). The adverse events reported in the RCTs were allocated to six categories: gastrointestinal, cardiovascular, respiratory, neurological, psychiatric, and sleep disorders. Three trials (37.5%) reported significant results for neurological disorders. Neurological adverse events were less frequent in saffron than sertraline (RR 0.13, 95% CI 0.17-0.93, p = 0.02) [16]. Levomilnacipran was consistently related to adverse neurological events in one placebo-controlled RCT (RR 12, 95% CI 1.84-78.37, p = 0.000) [19]. Neurological (RR 0.46, 95% CI 0.3-0.71, p = 0.000) and gastrointestinal (RR 0.54, 95% CI 0.31-0.96, p = 0.04) disorders were less common in tianeptine than escitalopram users [18].

Risk of bias

A high risk of bias was assessed for two studies (25%) [19,20], whereas two other studies 21,23 presented some concerns of bias risk in RoB-2 assessment. However, the risk of bias was low in three (37.5%) pharmacological [16-18] and one (12.5%) non-pharmacological interventions [22], respectively.

Discussion

An update of Krause and colleagues' systematic review [9] of all pharmacological and non-pharmacological RCTs published in recent years in the treatment of MDD in the elderly was conducted. With regard to pharmacological interventions, both vortioxetine, saffron and tianeptine reduced depressive simptoms in MDD older adults, although no significant differences in their efficacy were

Table III. Efficacy and dropouts.

Author	Intervention	Rating scale	Scores at Baseline		Scores at Completion		Response		Remission		Attrition rate	Dopouts due to adverse events	
			Treatment	Control	Treatment	Control							
			Mean, SD	Mean, SD	Mean, SD	Mean, SD	RR (95% CI)	P*	RR (95% CI)	P*	%	RR (95% CI)	P*
Ahmadpanah et al. [16]	Saffron (C. Sativus L.)	HRSD-17	21.12, 2.35	21.4, 2.86	9.92, 4.51	8.76, 4.52	8 (1.08 -59.32)	0.02	1.0 (0.61-1.63)	1.00	16,00%	0	0.49
Borhannejad et al. [17]	Vortioxetine	HRSD-17	30.6, 4.07	30.88, 5.93	21.52, 4.79	21.96, 6.1	1.02 (0.67-1.55)	1.00	0.6 (0.25-1.44)	0.38	16,67%	NA	NA
Emsley et al. [18]	Tianeptine	HRSD-17	26.7, 3.2	26.6, 3.5 (placebo)	13.3, 7.0	17.1, 6.9 (placebo)	1.39 (0.99-1.94)	0.07	NA	NA	11,25%	0.51 (0.13-1.98)	0.50
				26.7, 3.2 (escitalopram)		13.1, 6.6 (escitalopram)	0.86 (0.65-1.12)	0.27	NA	NA	NA	0.47 (0.12-1.83)	0.32
Krause-Sorio et al. [19]	Levomilnacipran	HRSD-24	NA	NA	NA	NA	NA	NA	1.41 (0.31-6.51)	1.00	51,72%	-	0.12
Ionson et al. [20]	Sahaj Samadi meditation	HRSD-17	14.16, 4.1	15.2, 4.4	NA	NA	2.58 (1.00-6.67)	0.06	0.24 (0.05-0.42)	0.03	15,66%	5.38 (0.66-44.04)	0.1
Roh et al. [22]	"Gold Medal Program" multidomain intervention	K-MADRS	31.6, 9.0	31.9, 7.9	NA	NA	NA	NA	NA	NA	NA	NA	NA
Solomonov et al. [21]	"Engage" psychotherapy	HRSD-24	22.9, 4.29	22.2, 4.45	NA	NA	NA	NA	NA	NA	NA	NA	NA
Verrusio et al. [23]	Physical activity with Human Body Posturizer (HBP)	GDS	8.5, 1.17	8.6, 1.26	5.2, 1.1	7.9, 1.0	NA	NA	NA	NA	NA	NA	NA

*HRSD -17 (24): 17 (24)-item version of Hamilton Rating Scale for Depression; K-MADRS: Korean version of Montgomery-Asberg Depression Rating Scale; GDS: Geriatric Depression Scale. *P: Two-sided Fisher's exact P. NA: Not Available.*

found when compared to sertraline and escitalopram, respectively. Focusing on adverse events, in comparison with sertraline, vortioxetine did not show any significantly difference, while saffron was associated to less neurological disorders. Neurological and gastrointestinal disorders were also less common in patients under tianeptine compared to escitalopram. Considering non-pharmacological interventions, response rates for one meditation-based trial were slightly higher than treatment as usual, but estimates had a poor consistence. Multi-domain intervention, reward-based psychotherapy and physical activity with HBP significantly reduced depressive symptoms in older patients compared to control groups.

In terms of response to treatment, Krause and colleagues' network-meta-analysis [9] showed a significant superiority for quetiapine and duloxetine compared to placebo [24]. Moreover, agomelatine, imipramine and vortioxetine outperformed placebo in pairwise meta-analyses, and there were also significant superiorities of several antidepressants compared to placebo in secondary efficacy outcomes [9]. With regard to non-pharmacological interventions, very limited evidence suggested that competitive memory training, geriatric home treatment group and detached mindfulness condition reduced depressive symptoms.

The small number of selected RCTs analizing different type of pharmacological interventions (except vortioxetine), does not allow a comparison with the results of the previous systematic review either in terms of efficacy or safety. Antidepressants keep to be effective in decreasing depressive symptoms in the elderly showing a significant superiority compared to placebo without, however, significant differences in comparison to controls (sertraline and escitalopram, respectively). Insufficient and not robust evidence supports the use of non-pharmacological approaches in treating MDD older patients.

Table IV. Adverse events.

	Intervention/ Control	Gastrointestinal disorders			Cardiovascular disorders			Respiratory disorders			Neurological disorders			Psychiatric disorders			Sleep Disorders		
		RR	95% CI	P*	RR	95% CI	P*	RR	95% CI	P*	RR	95% CI	P*	RR	95% CI	P*	RR	95% CI	P*
Ahmadpanah et al. [16]	Saffron/ Sertraline	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.13	0.17-0.93	0.02	NA	NA	NA	0	NA	0.49
Borhannejad et al. [17]	Vortioxetine/ Sertraline	0.82	-0.33-0.2	0.76	0.5	0.05-5.22	1	NA	NA	NA	1	0.07-15.26	1	NA	NA	NA	0.4	0.14-1.14	0.13
Krause-Sorio et al. [9]	Levomilnacipran/ Placebo	NA	NA	0.023	1.76	0.41-7.63	0.66	NA	NA	NA	12	1.84-78.37	0.000	NA	NA	NA	0.06	-0.05-0.17	1
Emsley et al. [18]	Tianeptine/ Placebo	0.85	0.45-1.59	0.71	NA	NA	NA	1.02	0.06-16.08	1	0.86	0.53-1.42	0.62	1.02	0.15-7.1	1	1.02	0.65-16.08	1
	Tianeptine/ Escitalopram	0.54	0.31-0.96	0.04	0		0.23	0.47	0.43-5.12	0.61	0.46	0.3-0.71	0.0003	0.31	0.06-1.52	0.16	0.31	0.03-2.97	0.36

NA: Not Available.

Along to the efficacy, particularly in older patients, differences in side-effects should be considered in drug choice. Feeling reluctant to use synthetic drugs frequently induce the elderly to take herbal products [25]. Above all, saffron has been already succesfully used for depressive symptoms [26] along to several somatic complaints, such as premenstrual syndrome, post-menopausal flashes, sexual dysfunction and infertility, and excessive snacking behaviors 27. The relatively low efficacy showed by antidepressants – only one out of nine people benefit from them [27] – and the risk of unnecessarily side effects, could increase attraction for herbal products, including saffron, in the older people.

This systematic review needs to be interpreted in the light of several strengths and limitations. Only RCTs were included and their quality was evaluated using a widely recognized tool for bias risk assessment. Most of the RCTs carefully reported study procedures and methodology. The scarce number of included studies reflects the selectivity of our inclusion and exclusion criteria. Study power was thoroughly affected by the short sample sizes. Consistent results were scant, and the effect sizes were often low. Some studies were at high risk of bias (Table I) and, not always, efficacy was the major outcome of the trials, raising concerns on selection bias risk [19].

The WHO proposition that there can be “no health without mental health” [28] is valid for everybody, but even more so for fragile groups, as the elderly, because of medical comorbidities, cognitive dysfunctions and polypharmacotherapies. Although significant effects for some pharmacological and non-pharmacological interventions in older patients, the overall MDD evidence is still scant and not robust. Further studies are needed in this vulnerable segment of population to confirm or refute our findings and consequent clinical recommendations [29].

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Appendix 1. MEDLINE Search Strategy.

SET	MEDLINE
1	Elder* OR old OR older OR "senior citizen" OR Aging OR aged OR "late-life" OR "late life" OR "late adult*" OR "late-adult*"
2	geriatri* OR geronto* OR psychoger* or geropsych*
3	older AND (65 OR 70 OR 75 OR 79 OR 80 OR 85 OR 90 OR 95) AND years
4	*Aged*
5	*Health Services for the Aged*
6	*Health Services for the Elderly*
7	Sets 1-6 were combined with "OR"
8	Depress* OR "unipolar depression" OR "major depressive disorder" OR MDD
9	(affective OR mood) AND (symptom* OR disorder*)
10	"Beck Depression Inventory" OR BDI OR Hamilton OR HAM-D OR "Montgomery-Asberg Depression Rating Scale" OR MADRS OR "Geriatric Depression Scale" OR GDS OR "depression rating scale" OR (operationali* AND diagnosis)
11	"ICD-10" AND "F33*"
12	*Depression*
13	*Depressive disorder*
14	*Depressive disorder, Major*
15	Sets 8-14 were combined with "OR"
16	antidepress* OR "anti depress*" OR MAOI* OR "monoamine oxidase inhibit*" OR ((serotonin OR norepinephrine OR noradrenaline OR "nor epinephrine" OR "nor adrenaline" OR neurotransmitt* OR dopamine*) AND (uptake OR reuptake OR re-uptake)) OR noradrenerg* OR antiadrenergic OR "anti adrenergic" OR SSRI* OR SNRI* OR TCA* OR tricyclic* OR tetracyclic* OR heterocyclic* OR psychotropic* Agomelatine OR Alaproclate OR Amoxapine OR Amineptine OR Amitriptylin* OR Amitriptylinoxide OR Atomoxetine OR Befloxatone OR Benactyzine OR Binospirone OR Brofaromine OR (Buproprion OR Amfebutamone) OR Butriptyline OR Caroxazone OR Cianopramine OR Cilobamine OR Cimoxatone OR Citalopram OR (Chlorimipramin* OR Clomipramin* OR Chlomipramin* OR Clomipramine) OR Clorgyline OR Clovoxamine OR (CX157 OR Tyrima) OR Demexiptiline OR Deprenyl OR (Desipramine* OR Pertofrane) OR Desvenlafaxine OR Dibenzepin OR Diclofensine OR Dimetacrin* OR Dosulepin OR Dothiepin OR Doxepin OR Duloxetine OR Desvenlafaxine OR DVS-233 OR Escitalopram OR Etoperidone OR Femoxetine OR Fluotracen OR Fluoxetine OR Fluvoxamine OR (Hyperforin OR Hypericum OR St John*) OR Imipramin* OR Iprindole OR Iproniazid* OR Ipsapirone OR Isocarboxazid* OR Levomilnacipran OR Lofepramine* OR ("Lu AA21004" OR Vortioxetine) OR "Lu AA24530" OR (LY2216684 OR Edivoxetine) OR Maprotiline OR Melitracen OR Metapramine OR Mianserin OR Milnacipran OR Minaprine OR Mirtazapine OR Moclobemide OR Nefazodone OR Nialamide OR Nitroxazepine OR Nomifensine OR Norfenfluramine OR nortriptylin* OR Noxiptilin* OR Opipramol OR Oxaflozane OR Paroxetine OR Phenelzine OR Pheniprazine OR Pipofezine OR Pirlindole OR Pivagabine OR Pizotyline OR Propizepine OR Protriptylin* OR Quinupramine OR Reboxetine OR Rolipram OR Scopolamine OR Selegiline OR Sertraline OR Setiptiline OR Teciptiline OR Thozalinone OR Tianeptin* OR Toloxatone OR Tranylcypromin* OR Trazodone OR Trimipramine OR Venlafaxine OR Viloxazine OR Vilazodone OR Viqualine OR Zalospirone
17	*Antidepressive Agents*
18	*Antidepressive Agents, Tricyclic*
19	*Adrenergic Uptake Inhibitors*
20	*Psychotropic Drugs*
21	*Monoamine Oxidase Inhibitors*
22	*Serotonin and Noradrenaline Reuptake Inhibitors*
23	sets 16-22 were combined with "OR"
24	Psychotherapy
25	Cognitive therapy
26	Behavioral therapy
27	Dynamic therapy
28	Collaborative care
29	Physical exercise
30	*Psychotherapy*
31	sets 24-30 were combined with "OR"
32	sets 23 and 31 were combined with "OR"
33	sets 7, 15, 32 were combined with "AND"
34	set 33 was limited from December 17th, 2017 to January 1st, 2021; English language; Aged: > 65 years; Study design: Randomized Controlled Trials (RCTs)

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Prevention and early intervention in mental health: a one-year analysis of activity from a Local Public Health Trust

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Summary

Introduction. Adolescence represents a critical period for the individual's psychic development, during which substantial neurobiological and psychosocial changes occur. It is estimated that about 70% of psychiatric conditions begin within 25 years of age and that nonspecific prodromal symptoms are already detectable several years earlier. The early identification and management of subjects at high risk of developing mental disorders or risk behaviors represent a priority within Mental Health Departments. In this study, data relating to the afference, the type of disorder identified, and treatments provided in a territorial Prevention and Early Intervention Service aimed specifically at subjects between 14 and 25 years residing in area of the Local Health Trust (ASL) Roma 1 were described.

Methods. Data concerning the services provided by the Unity from January 2020 to December 2020 to users residing in Municipalities referring to the (ASL) Roma 1 have been extrapolated from the following information systems: SISP 2000 and GDSM (territorial service and day center), SIPC- sr (residential structures).

Results. A total of 1149 subjects (53% female), representing the 1.2% of the 14-25 year-old population living within the territory of ASL Roma 1 were followed up by the service, with 486 (55% females) new outpatients during the 12 months considered. About 24% of new users had a VGF score of ≤ 50. The prevalent diagnoses for all subjects currently undergoing treatment were: neurotic disorders, 47%; personality disorders: 24%; affective disorders: 10%; psychotic disorders: 10%. One hundred thirty-three patients (11.6% of total users) were attending activities in the semi-residential service (day service), while 32 subjects were undergoing treatment in the residential facilities belonging to the unit. About 34.4% of patients reported use of substances, the most frequent being cannabis (83.3%). The ongoing COVID-19 pandemic was associated to a decrease of accesses during the first lockdown (march-april 2020), followed by a substantial rebound of referrals in autumn.

Conclusions. Evidence from the scientific literature and epidemiological data confirm the indication to intercept early and take charge of subjects at high risk or at the onset of a psychic disorder. This requires specific structures in non-stigmatizing contexts and with a multidisciplinary approach. The possibility of identifying early psychopathological and environmental risk factors is fundamental in the structuring of a timely and articulated intervention which, by limiting the duration of untreated pathology, can positively modify its trajectory and long-term outcome.

Key words: adolescence, young adults, psychiatry, community treatment, CAMHS, integrated healthcare

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Introduction

Adolescence represents a critical period for the individual's psychic development, during which substantial physical, neurobiological, emotional, and psychosocial changes occur.

Adolescence typically begins with the onset of physiological puberty and ends when an adult identity and behaviour are developed and integrated. The World Health Organization (WHO) defines "adolescents" individuals in the 10-19 years age group and "youth" the 15-24 years age group, while "young people" covers the age range 10-24 years [1]. In general, Authors tend to subdivide this lengthy period of development into "adolescence" (10-19 years) and "young adulthood" (20-24 years) [2]. However, there is only partial consensus on this matter among researchers, and age ranges defining adolescence are still debated.

Adolescents are faced with critical biological and psychological challenges. From a neurobiological perspective, there is increasing evidence that the adolescent brain undergoes major changes in the neural systems underlying several functions, such as emotion processing and control, motivation, cognition, interpersonal interactions, and risk-versus-reward appraisal. Modifications include, but are not limited to, changes in grey matter volumes, synaptic pruning, and myelination [3]. These processes start in childhood, become significant around 14 years of age, and continue throughout time until about 25 years of age, when remodeling and myelination of crucial brain areas, such as the prefrontal cortex, are completed. Alterations in these processes, together with environmental stressors (i.e., maltreatment, neglect, bullying, and substance use, among others), might undermine the physiological transition into adulthood and underlie the increased risk for the development of psychiatric disorders in this timeframe.

It is estimated that about 70% of mental health problems in adults started during childhood and adolescence, mostly between age 14 to 24, and earlier onset is associated to a more severe course of illness and chronicity [3-6]. However, most remain undetected and untreated until later in life [7]. Mental and substance use disorders are major contributors to health-related disability in children and youth, accounting for about ¼ of all Years Lived with Disability (YLDs) [8]. Half of all mental disorders starting in adolescence are usually preceded by non-specific psychosocial disturbances [9] that may persist for months or even years, delaying detection and intervention. Additionally, adolescents represent a population at higher risk of developing mental problems when facing severe social and environmental stressors, such as the recent, ongoing COVID-19 pandemic [10-12].

Mental health problems do not only affect young people and their family and friends, but also have deep implications for their social functioning. In Europe, 15 to 20% of adolescents have at least one psychological or behavioural problem, that often continue throughout adulthood and may become chronic, with eventual implications for global economy [13]. It is estimated that a yearly loss of 4% of the European gross national product is linked to the effects of mental health problems, such as absenteeism and reduced work performance [14]. Moreover, certain conditions, such as substance use, antisocial behaviour, conduct disorders, attention deficit/hyperactivity disorder (ADHD), and neurodevelopmental disorders, are associated with early involvement with juvenile justice system [15-16]. Since effective treatments during adolescence not only affect the duration of mental health episodes, but also reduce morbidity later in life and portend a better social and functional outcome [17], prevention and early identification and intervention are crucial [6]. Young people and their caregiver often fail to find adequate help for mental health problems. This is partly due to several issues, such as perceived and self-stigmatising attitudes to mental illness, limited access, and general lack of knowledge about mental health services [18]. In addition, adolescents have different care needs than adults and children, being right in the middle of their maturation end self-identification process. In 2002, the World Health Organization issued a statement that European Union member states are required to deliver tailored and adequate mental health care (MHC) interventions to adolescents in need of help. More specifically, member states need to ensure "age-sensitive MHC services (i.e., primary and specialised health care services and social care services) operating as integrated networks" [19]. To date, however, specialised MHC facilities for adolescents are lacking.

The current service configuration, with distinct Child and Adolescent Mental Health Services (CAMHS) generally treating patients until 18 years of age, and Adult Mental Health Services (AMHS), contributes to high rates of transition-related discontinuity of care. It has been estimated that between 25% and 49% of CAMHS service users will need transitioning to AMHS [20]. However, deficiencies in planning, organisation, and policy lead to a suboptimal transition process, and treatment gaps are particularly relevant for people affected by specific conditions, such as neurodevelopmental disorders [21]. Therefore, services allowing patients to be assessed in a structured and standardised way, in order to determine the on-going need for care throughout adolescence and early adulthood, will have the potential to improve treatment retention and, by delivering intensive, multidisciplinary, and tailored interventions during a crucial developmental timeframe, lead to better outcome and quality of life [22]. Finally, it is important to note that about 15–23% of children worldwide live with a parent with a mental disorder, and that these children are at increased risk to develop several mental and social issues, such as depression, anxiety, affect dysregulation, behavioral problems, reduced overall functioning, substance abuse, and lower occupational status [23]. These observations highlight the need for parent involvement in the treatment of adolescents.

Organization of a 14-25-year-old mental healthcare service in Rome

This dedicated public mental health service has been instituted within the Mental Health Department (MHD) of the Local Health Trust "ASL Roma1" in Rome, Italy. ASL Roma 1 provides healthcare to 6 out of the 15 administrative areas (*Municipi*) in which the city of Rome is subdivided (i.e., *Municipio* 1, 2, 3, 13, 14, and 15), serving more than 1 million inhabitants. Overall, this territory is extremely diversified in terms of sociodemographic characteristics and healthcare and social needs, requiring tailored interventions.

The service is aimed to adolescents and young adults (14 to 25 years old) living in the abovementioned areas. This age range has been defined to provide continuity of care across all stages of adolescence to adulthood, as defined by the WHO, overcoming the traditional separation between CAMHS and AMHS. This configuration then guarantees to specifically address patients' needs during a developmental timeframe characterized by profound neurobiological, psychological, and social changes, whose interaction shapes future health and functional outcomes. The service implements interventions aimed to both prevention and early identification and treatment of mental problems at their onset, reducing the duration of untreated illness, with a multidisciplinary approach. It provides care programmes to patients with major psychiatric disorders, including subjects of > 18 years with ADHD and autism spectrum disorders without cognitive impairment (formerly known as "high functioning"). Treatments include psychopharmacological and psychological (both individual and group) therapy, as well as psychosocial and vocational rehabilitation, and parental support. When appropriate, treatments are carried out conjointly with other mental health services, i.e., eating disorders and addiction centers. Prompt consulting of inpatients admitted to hospital psychiatric wards is also guaranteed.

The Unit comprises two independent outpatient health centres, located within the "east" and "west" areas of ASL Roma 1, providing assessment and therapeutic continuity to patients from Municipi 1 east, 2, and 3, and 1 west, 13, 14, and 15, respectively. Each center refers to an intermediate semi-residential structure (namely the Day Centre) designed to carry out psychiatric treatment, rehabilitation, and recovery and development of patients' social skills in an informal environment. Additionally, four residential facilities directly pertain to the Unit, providing long-term residential care in close cooperation with patients' referring therapeutic team. Residential structures are organized to provide assistance of different intensity, from round-the-clock support for severely impaired patients to relatively limited care for subjects with greater levels of functioning. Further activities of the Unit comprise psychiatric and psychological consultations for the juvenile detention center in Rome, as well as counselling for most of the high schools within the ASL Roma 1 territory.

Methods

We conducted a descriptive, retrospective review of existing medical charts on outpatients referring to a Prevention and Early Intervention in Mental Health Center of ASL Roma 1 between January and December 2020. Information was extracted from the electronic databases "SISP 2000" and "GDSM" (territorial services and day centers), and "SIPC-sr" (residential facilities). Data were anonymized and each patient was identified only by a numeric code automatically generated by the system. Age, gender, ICD-9-CM diagnosis, and Global Assessment of Functioning (GAF) scores [24,25] were extracted and analyzed. Diagnoses were attributed according to ICD-9-CM [26] codes and grouped as follows: Schizophrenia and Other Psychotic Disorders (ICD-9-CM: 295.x, 297.x; 298.x; 299.x), Affective Disorders (ICD-9-CM: 296.x), Personality Disorders (ICD-9-CM: 301.x), and Neurotic Disorders (ICD-9-CM: 300.x; 307.1; 308.x; 309.x; 311.x). Groups were chosen in line with Regional Health System requirements. Patients were also grouped by age (14, 15-19 and 20-24 years) according to World Health Organization's definition of "adolescence", and "young adulthood" [1]. The age of newly incident patients ("first ever") was calculated at the time of first evaluation, whereas the age of prevalent patients was calculated at 31/12/2020. The study was conducted in accordance with the recommendations of Good Clinical Practice guidelines and the Declaration of Helsinki (1964) and subsequent revisions. All subjects (or parents/tutors, if underage) gave written informed consent.

Results

Clinical and demographic characteristics

A total of 1149 subjects (53% female), representing the 1.2% of the 14-25 year-old population living in the territory of ASL Roma 1, was treated in the Unit during the considered 12-months. Four hundred eighty-six new outpatients (55% female) referred to the service during the same timeframe.

We observed an evident reduction of new accesses in March and April, followed by a progressive increase during the subsequent months, and in August, with a peak of new accesses during autumn. The course of new referral by month is shown in Figure 1.

The most frequent reasons for new referrals were: neurotic disorders, 262 (54%); personality disorders, 87 (18%); affective disorders: 46 (9%); psychotic disorders 40 (8%). The prevalent diagnoses for all subjects currently undergoing treatment were: neurotic disorders, 47%; personality disorders: 24%; affective disorders: 10%; psychotic disorders: 10%. Twenty-four percent of new users had a GAF score of ≤ 50, thus displaying severe symptomatology and functional impairment. Data are summarized in Tables I-V. Among prevalent subjects, 56 (4.9%) were diagnosed with conduct disorders (ICD-9-CM: 312.x) with a higher rate of

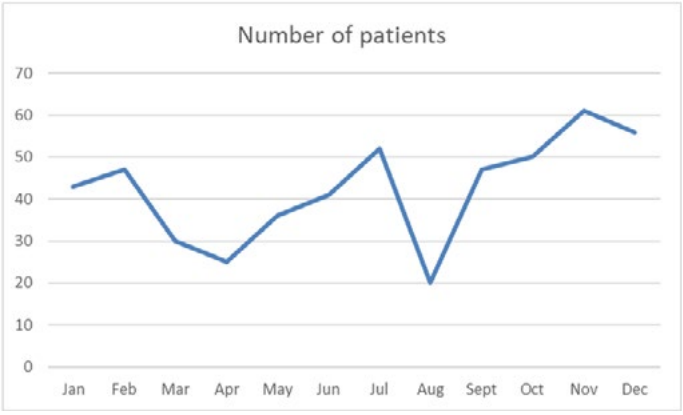

Figure 1. Course of "first ever" patients by month.

Table I. Incident patients (age, gender).

Age (years)	Gender					
	Male		Female		Total	
	n	%	n	%	n	%
14	6	3%	14	5%	20	4%
15-19	128	58%	148	56%	276	57%
20-24	82	37%	96	36%	178	37%
≥25	4	2%	8	3%	12	2%
Total	220	100%	266	100%	486	100%
%	45%		55%		100%	

males (n = 38, 67.8%; mean age 18.6 ± 1.9 years) over females (n = 18, 32.2%; mean age 18.7 ± 2.9 years). Additionally, 10 patients (0,87%; M = 9, F = 1; mean age 18.7±1.6 years) were diagnosed with ADHD (ICD-9-CM: 314.x), whereas 12 patients (1.04%; M = 9, F = 3; mean age: 21.7 ± 1.9 years) had autism spectrum disorders (ICD-9-CM: 299.0x, 299.8x). More than a half (55%) of newly incident patients self-referred to the service, while 19% were sent from other mental health services or were inpatients about to be discharged from hospital wards with subsequent need of continuity of care.

Seventy-three percent of subjects with psychotic disorders was treated by ≥ 3 different healthcare professionals (i.e., psychiatrist, psychologist, nurse, social worker, etc.), compared to 56% of affective disorder patients, 46% of personality disorder patients, and 21% of neurotic disorders patients. The number of healthcare professionals involved in treatments was also higher in patients with lower GAF scores, with ≥ 3 different healthcare professionals required in 65% of patients with GAF ≤ 50, regardless of diagnosis.

About 34.4% of patients (males: 62.7%; females: 37.3%) reported recreational use (at least once per week) of substances. The most frequently assumed drugs were cannabis (83.3%), alcohol (55.3%), cocaine and other stimulants (27.1%). However, only 11.3% of patients reporting frequent use of substances accepted to also refer to specific addiction services.

Finally, about 6% of patients was referred to the service from public security and justice Institutions, including juvenile/family court. Overall, a slightly higher rate (about 9%) of patients were involved in some kind of justice problems, from mild (i.e., drug possession) to severe (i.e., aggression), with a predominance of males (77%).

Day center and residential treatments

One hundred thirty-three patients (11.6%) were attending therapeutic-rehabilitation activities in the day centers (males: 49; 44%; females: 74; 56%), 52 of which entered the programme during the current year, while 32 subjects were undergoing residential treatment in facilities belonging to the unit. Thirty-one additional patients were treated in other residential centers throughout Italy; 86% of these patients were comorbid for substance use disorders.

Discussion

In this study, we describe demographic and clinical characteristics of patients treated in a mental health service

Table II. Incident patients (diagnosis, age).

Diagnosis	Age (years)									
	14		15 - 19		20 - 24		≥ 25		Total	
	n	%	n	%	n	%	n	%	n	%
Psychotic disorders		0%	12	4%	27	15%	1	13%	40	8%
Affective disorders	1	5%	28	10%	17	9%		0%	46	9%
Personality disorders		0%	55	20%	31	17%	1	13%	87	18%
Neurotic disorders	17	85%	151	54%	88	50%	6	25%	262	54%
Other disorders	1	5%	13	5%	5	3%		0%	19	4%
Non psychiatric	1	5%	16	6%	9	5%	1	13%	27	6%
Unknown/missing		0%	1	0%	1	1%	3	38%	5	1%
Total	20	100%	276	100%	178	100%	12	100%	486	100%

Table III. Incident patients (diagnosis, GAF scores).

Diagnosis	GAF scores											
	≤ 30		≤ 50		≤ 70		> 70		Unknown/ missing		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Psychotic disorders	9	39%	21	23%	7	2%	0	0%	3	11%	40	8%
Affective disorders	4	17%	13	14%	25	8%	2	6%	2	7%	46	9%
Personality disorders	3	13%	24	27%	52	17%	3	9%	5	19%	87	18%
Neurotic disorders	3	13%	26	29%	200	64%	23	71%	10	37%	262	54%
Other disorders	4	17%	4	4%	10	3%	1	3%	0	0%	19	4%
Non-psychiatric	0	0%	2	2%	16	5%	5	12%	4	15%	27	6%
Unknown/missing	0	0%	0	0%	2	1%	0	0%	3	11%	5	1%
Total	23	100%	90	100%	312	100%	34	100%	27	100%	486	100%
%	5%		19%		64%		7%		6%		100%	

Table IV. Prevalent patients (age, gender).

Age (years)	Gender					
	Male		Female		Total	
	n	%	n	%	n	%
14	2	0.4%	8	1%	10	1%
15-19	217	41%	258	42%	475	41%
20 - 24	265	49.6%	294	48%	559	49%
≥ 25	51	10%	54	9%	105	9%
Total	535	100%	614	100%	1149	100%
%	47%		53%		100%	

specifically aimed at adolescents and young adults. During the considered period (January-December, 2020), more than one thousand patients received healthcare, and almost 500 new subjects ("first ever") accessed clinical attention, with a slight prevalence of females.

The number of monthly accesses was not constant, with an evident decrease during march and april and a high-point in autumn. This reduction overlaps with the outbreak of COVID-19 pandemic in Italy and subsequent implementations of emergency containment measures from the Government. During this timeframe, regular clinical activities were guaranteed, although with some modifications in line with Government dispositions. However, many patients cancelled their appointments, postponing or waiving treatment. Motivations for this behaviour are unclear. It might be hypothesized that some people gave up reaching the center out of fear of contagion, whereas others might have changed their perception of their own mental status and need for immediate care. However, these remain speculations, and conclusions cannot be drawn. Referrals' decrease in august, in contrast, was predictable and constant over the years, being related to partial reduction of clinical activities and to highest rate of people leaving the city for summertime holydays.

Table V. Prevalent patients (diagnosis, GAF scores)

Diagnosis	GAF scores											
	≤ 30		≤ 50		≤ 70		> 70		Unknown/ missing		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Psychotic disorders	22	39%	64	20%	31	4%	1	2%	11	15%	129	10%
Affective disorders	9	16%	47	14%	58	8%	4	7%	7	10%	125	10%
Personality disorders	10	18%	105	32%	167	22%	6	10%	17	24%	305	24%
Neurotic disorders	7	13%	85	26%	444	59%	41	71%	20	28%	597	47%
Other disorders	7	13%	17	5%	21	3%	1	2%	2	3%	48	4%
Non-psychiatric	1	2%	6	2%	21	3%	5	9%	9	13%	42	3%
Unknown/missing	0	0%	2	1%	14	2%	0	0%	6	8%	22	2%
Total	56	100%	326	100%	756	100%	58	100%	72	100%	1268	100%
%	4%		26%		60%		5%		6%		100%	

The main reason for treatment-seeking was neurotic disorders (i.e., anxiety disorders, panic disorders), a result in line with previous reports [27]. This might also partially explain the observed gender differences, since neurotic disorders tend to be more frequent in females.

About 5% of our sample was diagnosed with conduct disorder, while ADHD and neurodevelopmental disorders were less represented. In all three groups, we observed a predominance of males, a result in line with other reports [28-30]. Despite increasing awareness on these conditions is leading to better identification, the overall number of patients remains quite low. This might be partially due to the fact that the majority of these patients is usually first treated in CAMHS and might be either discharged at the end of treatment, or lost during transition to other care facilities.

More than a half of help-seeking patients was self-referred. A significant rate (about 1/5) reached the service from either other healthcare providers belonging to the Trust or from hospital psychiatric wards, thus indicating a good continuity of care between different services.

Most patients (75,3%) were offered a combined treatment with at least two different healthcare professionals involved. In particular, psychotic disorder patients displayed a high rate of service utilisation, with more than 70% of them being treated by teams of 3 or more professionals.

In our sample, 65% of patients with GAF ≤ 50 required treatment from at least 3 different healthcare professionals. Although this might appear quite intuitive, it is still interesting to note that patients with "non severe" diagnosis account for about one third of all patients with GAF ≤ 50, highlighting the importance of functional impairment in terms of healthcare burden and service utilisation. Many neurotic or conduct disorder patients might display significant difficulties in relations and school performance, and might therefore require intensive, multidisciplinary interventions to prevent social isolation and school dropout.

More than 1/3 of patients reported regular consumption of substances of abuse, especially cannabis (83.3%) and alcohol (55.3%). Interestingly, the rate of cannabis use in our sample is in line with previous reports on Italian secondary school students [31], hinting at a dramatic diffusion of cannabis consumption within this age range regardless to mental health status. Substance use among adolescent represents a significant public health problem. According to the latest ESPAD report, substance use has risen over the years, with earlier age of first intake and a progressive narrowing of gender gap, as females increased drug and alcohol consumption [32,33]. Comorbidity of psychiatric disorders and substance use leads to increased symptom severity, worse course of illness, lower functioning, and detrimental outcomes. Additionally, epidemiological data show that about one third of underages accessing Emergency Departments in Lazio were diagnosed with substance use disorders [34]. However, despite this evidence, only a minority of patients with co-occurring substance use refers to specific addiction services. This might be due, at least in part, to insufficient awareness on this problem and its consequences. Stigmatization towards addiction care services might also play a role.

About one out of 10 patients was involved in some kind of justice problems. Although increasing evidence points out that psychiatric patients are not more likely to commit crimes [35], associations have been found between certain psychiatric diagnosis (i.e., ADHD, antisocial personality disorder, conduct disorders, substance use, and neurodevelopmental disorders) and higher rate of contact with juvenile justice systems [15,16]. In this perspective, early identification and treatment of these conditions might prevent at-risk behaviours and involvement in illegal activities, offence, and crime, other than representing a crucial step in effective rehabilitation and social reintegration.

Young adulthood is a unique and critical period of development during which unmet health needs and disparities in access to appropriate care are high. Although it is well known that most mental and substance use disorder onset in adolescence, early identification and treatment might be challenging. Subjects might display several non-specific prodromic symptoms before a clear diagnosis can be made, leading to delays and undertreatment. Additionally, clinical presentation is often complex and comes at the interplay of many different neurobiological and environmental factors, each playing a significant role in determining future trajectories of the illness. Several alternative classification criteria have been proposed to better address this variety of presentations (i.e., internalizing vs externalizing disorders), focusing more on psychopathological dimensions, such as impulsivity and emotional dysregulation, and overall functioning. Finally, clinicians must face significant new challenges, like the substantial increase of "newly emerging" mental disorders, such as Internet, gaming, and smartphone addictions, or severe social retirement (i.e., "hikikomori"), for which standardized treatments are still not available and are often associated with high rates of school dropout and "NEET" (*Not in Education, Employment, or Training*).

Although in recent years many international organizations, such as WHO, repeatedly pointed out the urgent need for implementing mental health care addressing adolescents' and young adults' specific needs, and substantial efforts have been made in many Countries, the availability of dedicated services is still insufficient. This is also associated with a significant rate of dropouts and inadequate deliver of care during transitions from CAMHS to AMHS. Another critical aspect is the reduced availability of psychiatric wards for underages in hospitals, as well as of dedicated residential facilities, that limit both the safe management of critical episodes and the possibility of effective long-term rehabilitation.

Improvement of the general health, family conditions (e.g., through parental support) and school environment has been demonstrated to show beneficial effect on youth mental health. Preventive interventions require integrated socio-sanitary policies aimed at promoting healthy life-

styles of adolescents and increasing awareness of their behaviours. Finally, epidemiological surveys should be carried out, in order to inform appropriate resource allocation and support policies that address mental health needs of this population [36].

This study has some limitations that must be acknowledged. First, the quality of data, which depends on a correct data entry from the single professional. Consistency on attribution of diagnosis and GAF scores could not be evaluated. The same patient might require more than one treatment over the years and might be attributed different diagnosis as the disease unfolds, leading to a discrepancy between the number of subjects treated and the number of active treatments/diagnosis among prevalent patients. Due to characteristics of the informatic system, information about comorbidity is limited. Finally, these results relate to a specific group of patients (14-25 years old subjects living in a defined urban area), which limits their generalizability to other clinical populations.

Conclusions

This descriptive study outlines the clinical characteristics and utilisation rates of patients referring to a center specifically designed to offer mental care to adolescents and young adults, delineating an accurate picture of a service which is both innovative in its organization and significant in terms of healthcare provided.

Implementation of mental health services specifically aimed to adolescents and young adults is crucial for delivering adequate support throughout this critical neurodevelopmental period, when the early identification and availability of tailored, multidisciplinary interventions might prevent the onset of severe mental disorders and dramatically modify illness trajectories, reducing chronicization. Working in network with additional healthcare providers, including hospitals, other mental health services (i.e., CAMHS, AMHS, eating disorders services, addiction services, etc.), and GPs, is crucial to deliver comprehensive treatments and to avoid dropouts during transitions between services. Additionally, healthcare centers easily accessible, designed to address youth specific needs, and deeply integrated with other public Institutions within the community (i.e., schools) might reduce stigmatization and encourage referrals, reaching a wider number of subjects and effectively promoting well-being.

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Transcranial Magnetic Stimulation to treat Substance Use Disorders and Behavioral addictions: the state of the art

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Summary

Objectives. Substance Use Disorders (SUDs) are characterized by a high health and social impact, care burden, and frequent negative outcomes, especially due to the few pharmacological treatments available, the high relapse rate and poor pharmacological compliance. In this scenario, TMS is increasingly being studied as a tool to treat the neurbiological dysregulations underlying SUDs in an innovative way. The aim of this non-systematic review is to analyze the main and most significant applications of Transcranial Magnetic Stimulation in the field of addiction.
Materials and methods. A PubMed search was conducted using the keywords: "Transcranial Magnetic Stimulation; and Substance Use Disorder; Behavioural Addiction" in December 2020. Only original article written in English dealing with the treatment of cocaine, opioids, alcohol, cannabis and gambling disorder were included.
Results. Three hundred and thirty-four article were found. Based on the current evidence, rTMS can be classified as probably effective in the treatment of addiction, with promising effect size for high frequency rTMS stimulation protocol of the DLPFC mainly in cocaine/stimulant use disorders, and with some noteworthy pilot data in the area of gambling disorder. Double-blind, sham-controlled study design are mostly needed in order to confirm these potential benefits.
Conclusions. Future research should identify potential parameters (i.e., duration, number of stimulation treatments, stimulation frequency, intensity, brain region of target) of stimulation in rTMS studies for the most effective and safe treatment of drug addiction. The personalization of rTMS treatments, as well as the optimization of stimulation protocols, are the main issues that will involve future research in this area.

Key word: Transcranial Magnetic Stimulation, Substance Use Disorders, Behavioral addictions

Introduction

Substances use disorder (SUD) is defined, in the DMS-5, as "*a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems*" [1]. In clinical practice it could be described as a chronic pathology with frequent relapses, compulsive seeking behavior, presence of a negative emotional state (e.g., dysphoria, anxiety, irritability, anhedonia) and loss of the ability to control the assumption [2]. This aspect in particular

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highlight a dopaminergic dysregulation in specific neural circuits [3]. A key role in the addiction cycle is played by the prefrontal cortex (PFC), involved in learning reinforcement and craving [4]. The function of PFC was deeply studied in preclinical works: a specific lesion of PFC carry to a loss of the inhibitory control, one of the main domain involved in substances seeking behaviors 5. Above the function of the PFC itself, all the dopaminergic system is primary involved in the anticipation and reward motivation [6]. Studies using positron emission tomography have shown that patients with SUD have a reduced number of striatal D2 receptors and a lower dopamine release than the general population [7]. This dopaminergic dysregulation is at the base of the "*incentive awareness theory*": a greater reactivity of the mesolimbic system is linked with drug addiction and craving 8. All these neuronal imbalance are reinforced by chronic use of the substance, which leads to dysfunctional synaptic and receptor adaptation [2].

One of the main concerns of clinicians about SUD is their treatment: very often there are only symptomatic drugs or substitutive therapy, with limited efficacy as demonstrated by high long-term relapse rates [9]. Nowadays, one of the most promising (and most investigated) therapy is Transcranial Magnetic Stimulation (TMS). The TMS protocols provide the administration of magnetic impulses generated by the passage of the electric current inside a copper coil. The intensity (measured by a percentage of the resting motor threshold; RMT) and frequency of the magnetic pulse, as well as the duration of the protocol, the target area and the shape of the coil used are the main parameters that characterize the different TMS treatments [10]. The protocols delivering several pulse trains (repetitive TMS; rTMS) in few minutes of stimulation are the most used worldwide [11]. TMS has already been approved for the treatment of resistant depression [12] using an high-frequency protocol (10 Hz) with 75 trains (40 pulses per train) stimulating at 120% of RMT the LDLPFC for about 19 minutes. Always in psychiatric field, deep TMS stimulation of anterior cingulate cortex was approved for obsessive-compulsive disorder with a 20 Hz protocol with 50 trains (2 sec duration) at 100% of RMT for a total of 2000 pulses administrated per session [13]. TMS stimulation was also approved by FDA for the treatment of headache with aura [14].

The rationale for rTMS in SUDs and other behavioral addictions has its roots in preclinical studies. A work conducted by Chen and coll. on 2013 [15], highlighted that the optogenetic stimulation of PFC in rats could reverse cocaine-induced prefrontal hypofunction, and blocked drug-seeking behaviors [16,17] in compulsive cocaine-seeking rats. The PFC of rats has its homologous in the dorsolateral prefrontal cortex (DLPFC) in humans [18]. Despite consensus on this matter is still missing, due to the relevant large anatomical diversity between the rodent and the human frontal/anterior cortices, this parallelism provides a first rationale of the non-invasive stimulation of this area with TMS procedures. Another reason for targeting the DLPFC is based also on the key role that this brain region plays in decision making processes [19]. Addiction is associated with increased impulsivity and impaired risky decision-making [20]. These decision-making processes in addiction can be modulated by rTMS on the DLPFC enhancing inhibitory control, which may lead to a reduction in the use of substances. Therefore, the stimulation of the DLPFC by high frequency pulses should increase its activity and its inhibitory control function. In particular, with drug-addicted subjects, this treatment should increase DLPFC function implementing the possibility to control craving and to cope it.

A further aspect to consider is that targeting prefrontal areas via TMS also affects dopaminergic neurotransmission. Strafella and coll. [21] found that high frequency rTMS on the prefrontal cortex in humans induces subcortical release of dopamine in caudate nucleus, whereas Cho and Strafella [22] showed that rTMS over the left DLPFC modulates the release of dopamine in anterior cingulated cortex and orbitofrontal cortex in the same hemisphere.

Finally, rTMS could also exert their effects modulating the expression of neurotrophic factors, such as BDNF, an active regulator of synaptic plasticity, within cortical and subcortical areas (Cirillo, Di Pino et al., 2017). More recently, non-synaptic events have been suggested as mediators of rTMS long-term effects, including plasticity-related gene expression and neurogenesis [23,24].

Given these evidences in the scientific literature, the aim of this work is to analyze the main and most significant applications of TMS in the field of addiction.

Materials and methods

A PubMed search was conducted using the keywords: "*Transcranial Magnetic Stimulation;Substance Use Disorder; Behavioural Addiction"*. No temporal criteria were applied. The research, conducted on December 2020, yielded 384 useful results. The most significative articles, written in English, concerning the treatment with TMS of the main substances of abuse (cocaine, opioids, alcohol, cannabis) were therefore selected. All non-original articles (such as reviews) were excluded from this non-systematic selection.

Results

Cocaine Use Disorder

Chronic cocaine use is among the most difficult substance-use disorders to treat. Nearly 1 in every 7 people seeking treatment for drug abuse is dependent upon cocaine (Abuse N.I.O.D, 2010) and short-term cocaine relapse rates can reach 75% [25]. Advances in understanding the neurobiological underpinnings of cocaine use disorders have unraveled that chronic cocaine use causes damage and changes in the PFC [26], including significant

brain volume reduction [27,28], cortical hypoactivity [5,29,30], impairment in executive functions, and dysregulation of neurotransmitters systems [31-33]. Thus, targeting the PFC via TMS appears to be a promising intervention. An open label study with a sample of 36 subjects, analysed the effect of high-frequency TMS (15 Hz) on the LDLPFC with a low number of pulse (600 pulses; 100% RMT) per session. This study lead to a significative reduction in intensity of craving for cocaine [34]. However, one of the first studies strongly highlighting these evidences is the one conducted by Terraneo and collaborators. In this work the LDLPFC was stimulated with rTMS (15 Hz, 2400 pulses / session, 40 trains of 60 pulses each) for two consecutive weeks. This treatment lead to an improvement in cocaine assumption (traceable on urine control tests) and craving [35]. In more recent time, the works of Zhang and coll. [36] and Pettorruso and coll. [37] offered more evidences on the efficacy of TMS to treat CUD. In the last of these studies, nine of sixteen patient stimulated with the same parameter of Terraneo and coll. [35] did not report any cocaine assumption after 4 treatment weeks. Also other psychiatric dimensions (depressive symptoms, anhedonia, and anxiety) improved after TMS stimulation.
The stimulation of right DLPFC (RDLPFC) was investigated in a study conducted in 2007 by Camprodon and coll. [38]. This randomized crossover trial offered a first insight on the efficacy of the RDLPFC stimulation (10 Hz; 90% RMT) with a population of six male patient underwent two session of rTMS, one per week. In addition to the craving for the substance as assessed with the VAS scale, other variables (e.g. anxiety, happiness, sadness) were also evaluated

Opioid Use Disorder

Recent increases in opioid addiction, opioid-related morbidity, and opioid-related mortality have been reported in both USA and Europe. While the number of opioid prescriptions doubled in Europe during the last 10 years, nowadays every day 130 patients die from an overdose of prescription opioids each day in USA [39]. Treatment for opioid use disorder typically requires acute detoxification and/or opioid maintenance treatment. The two primary treatments for opioid use disorder (methadone, buprenorphine) are designed for long term opioid maintenance therapy. Methadone is a mu-opioid receptor agonist whereas buprenorphine is a partial mu-opioid receptor agonist (mu agonist-K antagonist).
In the field of Opioid Use Disorder (OUD), the investigation around the effectiveness of TMS is difficult and susceptible of major side effects. Given that opioid withdrawal increases brain sensitivity to TMS induced seizures, this device has not been deeply examined in opioids-dependent patients [40].
Few studies have investigated the anti-craving efficacy of TMS by stimulating LDLPFC. A case report of a heroin-dependent subject conducted on 2020 [41], showed that seven rTMS session in 3 weeks (10Hz rTMS, 100% RMT) can significantly reduce craving. In another sham-controlled study [42], the efficacy of high frequency rTMS (10 Hz, 100% RMT) was studied on 20 subjects (10 for each group) after five session and then after other four days of stimulation. A significative improvement in craving symptomatology was highlighted .
Moreover, it may be interesting to notice that Nucleus Accumbens (NAcc) stimulation with Deep Brain Stimulation (DBS) has been reported to significantly reduced heroin consumption and/or craving in single cases [43-45].

Alcohol Use Disorder

There are currently four FDA-approved pharmacotherapies for alcohol use disorder – disulfiram, oral naltrexone, extended release injectable naltrexone, and acamprosate. These pharmacotherapies have been approved based on their effects in increasing abstinence more than placebo. Although these pharmacotherapies, also in combination with psychotherapies, have shown some positive findings, relapse rate are still high in patients with Alcohol Use Disorder (AUD) [46]. One of the first brain stimulation of subject with AUD was conducted in 2010 by Mishra and coll. and reported a significative anti-craving action of a 10 Hz rTMS protocol. In this sham-controlled trial 45 subjects underwent 10 daily stimulation on RDLPFC [47].
Some anti-craving effect was also showed by the stimulation of the dorsal anterior cingulate cortex using a double-cone coil [48]. A recent study conducted in 2017, analyzed the availability of DAT after four weeks of rTMS sessions in a sham controlled study. In this work, only the patients receiving active stimulation had a modulation in DAT availability, suggesting a potential role of rTMS as anti-craving tool [49].
However, there are several studies that do not show efficacy of the rTMS treatment for AUD. In 2011, Höppner and coll., investigated the efficacy of rTMS (20 Hz) on LDLPFC. In this sham-controlled trial, 19 subjects were enrolled (10 active and nine sham stimulation) and underwent rTMS stimulation for 10 days. No signifivative improvenment in craving levels for alchol was showed [50]. In the sham-controlled single-blind study of Herremans and coll. in 2012, 36 alcohol-dependent inpatients, underwent a single rTMS stimulation (20 Hz, 110% RMT, 40 train with a 12 s inter-train interval) above the RDLPFC before the discharge from a community for the weekend. Also in this study there was no significant effect of rTMS on craving for alcohol [51].

Cannabis Use Disorder

Cannabis is the most recreationally used drug worldwide: recreational users were approximately 3.8% of the world population in 2017. As the number of cannabis users has increased, the potency of cannabis expressed as the amount of THC increased as well. At the same time, legalization policies lead to decreased risk perception.

The risk to develop a Cannabis Use Disorder is around 10% for recreational users and is linked to increased risk of psychiatric and neurological illnesses [52].
Only one recent open label study investigated the efficacy of rTMS in Cannabis Use Disorder (CaUD) [53]. Nine patients underwent 20 sessions (two weeks) of rTMS stimulation (10 Hz, 120% of RMT, 4000 pulses 5s-on,10s-off) above the LDLPFC. Only three patients completed the entire protocol, and no significant improvement in craving symptomatology was highlighted in this study [53].

Gambling disorder

Non-substance-related addictive disorders are frequently comorbid and share some neurobiological substrates and behavioral manifestations of substance-related addictive disorders. This is particularly true for gambling disorder. It is thus an important question whether neuromodulation could change these neurobiological vulnerabilities, and thereby have clinical value for non-substance addictive behaviors as well [54].
Gambling disorder (GD) was recognized as the first behavioral addiction, and as such was reclassified within the category of "Substance-related and Addictive Disorders", in the Diagnostic and Statistical Manual of psychiatric disorders (DSM-5) in 2013. In the ICD-11, gambling disorder was classified within the same super-category of disorders due to substance use or addictive behaviors. In the DSM-5, gaming disorder was placed in the Appendix as a condition requiring more research. There is abundant evidence on similarities between GD and SUDs regarding genetics, neurobiology, psychological processes, and effectiveness of psychological treatment [55]. In GD, a neurocognitive profile showing diminished executive functioning compared to healthy controls (e.g. diminished response inhibition, cognitive flexibility) was related to differential functioning of the DLPFC and anterior cingulate cortex (ACC), both part of the cognitive control circuitry [56,57]. Moreover, increased neural cue reactivity and associated self-reported craving are present in the striatum, orbitofrontal cortex and insular cortex in gambling disorder compared to healthy controls. These abnormalities in frontostriatal functioning in GD warrant the question of whether NIBS may be a promising add-on treatment for gambling disorder and other non-substance-related addictive disorders [58]. Currently, a very limited number of studies explored TMS correlates in GD. For instance, in a single session pilot study in nine problematic gamblers, high frequency rTMS reduced desire to gamble, whereas cTBS reduced blood pressure, but had no effects on gambling desire [59]. Furthermore, the authors reported no effects on impulsive behavior (delay discounting) and Stroop interference were evident. Also in a sham-controlled cross-over high-frequency rTMS study (left DLPFC), a single session active rTMS diminished craving compared to sham rTMS [60]. Yet in another trial, low-frequency rTMS over the right DLPFC had similar effects as sham stimulation on craving, thus suggesting the occurrence of placebo effect [61]. Recently, a sustained effect (six months) was described in a GD subject [62], along with a modulation in dopaminergic pathways. In addition, a reduction in gambling-related symptoms has been observed also in GD-CUD comorbid patients [63]. Although preliminary, rTMS shows promise in restoring gambling-related pathophysiological alterations, deserving further investigations in well-powered controlled studies. Moreover, rigorously conducted clinical trials are needed to investigate optimal rTMS protocols with the potential to improve cognitive functioning, to diminish craving, and/or to reduce gambling behaviors/relapses in GD. Finally, if we consider GD as a disorder characterized by loss of control with respect to striatal drives such as craving, urgency for gambling and reward-seeking behaviors, then neuromodulation could be utilized as an intervention aimed at enhancing both cognitive control and the regulation of the reactivity to natural rewards.

Safety of rTMS in SUDs

The major concern about TMS safety in the treatment of SUDs is related to the risk of inducing seizures [64]. Currently, no evidence supports a TMS-related increased risk of serious or non-serious adverse events in the treatment of addictive disorders [64]. Nonetheless, increased vigilance is always warranted when theoretical concerns exist or in specific patient subgroups with limited prior data. From a safety standpoint, while rTMS has been recently established as a safe therapeutic tool, it is important to take into account that the application of rTMS in addiction is still a nascent field. Some concerns regard the possibility to induce seizures, an event that is frequently described in SUDs. Any medical and pharmacological factor independently increasing the risk of a seizure (e.g., stimulant use, alcohol use/withdrawal, benzodiazepine/barbiturate use/withdrawal, opioid use, tramadol use, bupropion in nicotine treatment, other psychopharmacological treatments used for comorbid psychiatric disorders) can in theory synergistically increase brain sensitivity to TMS induced seizures and should be taken into account.

Discussion and Conclusion

Building on data from major depression and OCD (for which TMS is currently FDA approved), we are now beginning to build a foundation of knowledge regarding rTMS utility as a tool to change smoking, drinking, and cocaine use behavior. These data provide a summary of the use of rTMS in the field of addiction. While for OUD and CaUD there are few studies in the literature reporting the efficacy of TMS protocols, for AUD the studies show controversies. Probably these results are affected by the concerns of stimulating these patients, given the increased risk to have seizures with TMS during the alcohol detoxification

phases, for which particular attention is required [65]. Many of the studies regarding the treatment of SUD deal with cocaine addiction. In this field rTMS can be classified as useful anti-craving tool, with promising effect size for high frequency rTMS stimulation protocol of the LDLPFC. Also, in the treatment of GD, TMS treatment could be considered as an innovative and promising technique.

One of the main evidences highlighted in this review is the high heterogeneity of the parameters used and in particular: frequency of stimulation (high vs. low frequency); intensity; number of stimulations; stimulation area and laterality; typology of coil; concurrent psychopharmacology; specific days of treatment. This high variability makes very hard to detect a specific protocol that could guarantee a better outcome [58]. These concerns about laterality 66 are highlighted by the difference in anti-craving efficacy considering CUD and AUD: in the former, the greatest benefits are obtained by stimulating the LDLPFC, in the latter the RDLPFC.

Moreover, the number of days of stimulation play a crucial role in the efficacy of rTMS. In general, repeating stimulation over multiple days has demonstrated efficacy in various clinical applications, as happen for the treatment of depression [67]. In addition, there are few study with a long follow up period; this is a serious limitation, given that addiction is a chronically relapsing disorder [58].

"When to stimulate" is another issue that need to be better defined. As suggested in a recent consensus paper [58] there are four distinct time intervals at which rTMS/tDCS interventions were administered: (1) before the participant sought standard treatment, (2) while the subject was treatment seeking but before undergoing standard treatment, (3) within the first month of standard treatment (mainly detoxification and stabilization) and (4) after the initial recovery period (more than one month). If the definition of these time intervals appears to be clear, we are still far to know which intervention would benefit the most in terms of efficacy. For safety reason it is of course advisable to avoid the intoxication phase and the early detoxification, specifically alcohol and opiates withdrawals.

The role of "Outcome Measures" is also of high relevance [58]. Most of the studies used craving as their primary outcome measure. Self-report on a visual analogue scale (VAS) was the most frequently used craving measure whereas few studies used objective measures such as urine drug tests or breath analyzers. Although a reduction or elimination of the consumption of the drug is the ultimate endpoint for clinical trials research, there are also many other behavioral and biologic variables that have been studied extensively and are considered meaningful surrogate endpoints for patients seeking treatment for SUDs (e.g. heightened reactivity to predictive drug cues, perseverative responding, delayed discounting for the drug, response to stress, narrowing of the behavioral repertoire) [68].

Neuromodulatory treatments have also been used for comorbidities with SUDs [58]. Overlapping neurobiological substrates between SUDs and psychiatric disorders (Dunlop et al., 2017) have been widely reported. One group studying smokers with schizophrenia demonstrated that rTMS reduced cigarette cravings compared to sham 69. Another group using rTMS for comorbid dysthymia and alcohol use disorder, showed decreased alcohol consumption with rTMS 70. Perhaps a dual benefit of brain stimulation treatments targeting underlying neurobiological factors in SUDs may also extend to deficiencies found in other psychiatric disorders (i.e., nicotinic acetylcholine receptor deficits found in schizophrenia patients, associated with both higher smoking rates and cognitive dysfunction) [71].

The outcome observed is still far to be considered fully satisfactory. Variability in cortical excitability may also be linked to genetic characteristics, in the same way that responses to medications can be influenced by genetic variability [72]. A research domain criteria approach able to identify the specific endophenotype that could be better benefit from rTMS is going to be the goal of NIBS in the next years.

This summary of the literature on rTMS treatment of SUDs, although bringing very interesting clinical potentials, highlights the need to identify potential parameters of stimulation in order to produce reliable efficacy data to the already well-investigated safety of TMS [73].

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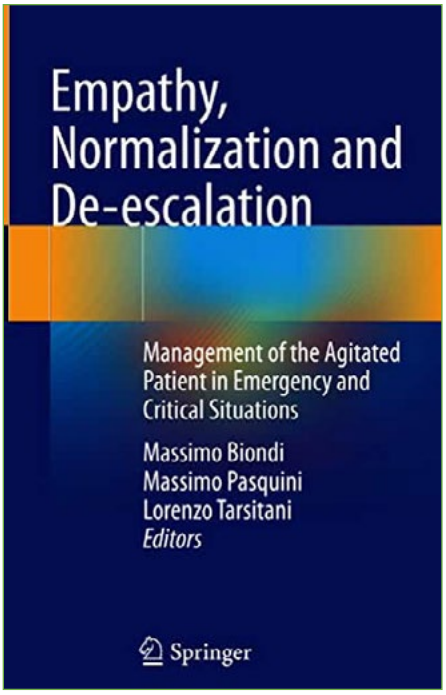
Book Review

Empathy, Normalization and De-escalation
Management of the Agitated Patient in Emergency and Critical Situations

Massimo Biondi, Massimo Pasquini, Lorenzo Tarsitani



In this book we aimed to provide a full presentation of the main techniques and the practical skills to manage an agitated or aggressive person in clinical and nonclinical settings. Later we introduced an easy and practical course for medical and paramedical staff for more than 10 years now. When an healthcare personnel assist an aggressive patients the main rules are: to know how to connect with him, how to calm him and lead to a negotiation by means of specific de-escalating words. We describe several specific skills such as a specific model of communication in 3 steps: how to engage the aggressive/ agitated person with a real empathic communication; how to normalize and de-escalate (the END method: Empathy, Normalization, De-escalation). It is a sequence, brief and specific, it is not based on generic reassurance or suggestion 'to be calm now' or similar: and every component of the END Method has its theoretical background, neural correlates, and practical procedures to act. The rationale is based on the ability to manage feelings, thoughts and manifested behaviors in order to prevent aggression and violence, but also to built up a therapeutic alliance in several settings, with the aim of reduce the forced hospitalizations. The skill of this professional communication is not an innate one; it can, however, be learned and systematically applied. Many clinicians practiced it and they found out very useful and innovative to learn communication techniques in hard situations. Indeed, talking to a scared or aggressive person is difficult, but this ability could be learnt. This textbook is constituted by two distinctive parts: the knowledge component, that regards theory and the primary non verbal and verbal communication skills; the practical component, that as to do with the ability to choose the right words in the right time with the right tone with the pivotal respect of listening to what the person is talking about without judgment. Our thinking as authors derived from our experience as psychiatrist but also from the experience of teaching these concepts to hundreds of colleagues. As editors we have retained the virtue of keeping these abilities simple.