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Editorial

Società Italiana di Psichiatria

49° Congresso Nazionale della SIP, Genova 12-15 ottobre 2022: finally the SIP's National Congress in presence

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[1] Presidente SIP; [2] Past President SIP

Massimo di Giannantonio

Enrico Zanalda

We are really looking forward to meeting next October in Genoa for the 49th National Congress, postponed by two years due to the Covid 19 pandemic. The Congress was initially scheduled from 1 to 4 October 2020, postponed a first time to autumn 2021, a second time to May 2022, and finally organized to the current date 12-15 October 2022. These forced postponements effectively extended the term of office of the current executive of the Italian Psychiatric Association (SIP) by one year. This election postponement has led to some tensions within the executive and uncertainty as to the composition of the next one. With goodwill and a spirit of cooperation, agreement was reached on a single list of candidates, leaving the choice of the next hospital president to the members' meeting.

Whoever of the two candidates is elected will have the support of the other elected members in the unitary list that was built through a mediation of the wishes of the territorial component. The national congresses have always been an interesting time for scientific discussion and the society's strategy, and the elective congress has also been a time for renewal and an increase in new members. During these 4 years of pan-demia, the scientific society has wanted to be present with numerous initiatives to support all mental health operators, I recall the distribution of IPDs in 2020 supported by Otzuka pharmaceuticals and the realisation of specialist telephone support for operators in agreement with TIM, the publication of behaviour guidelines during the various phases of the pandemic in cooperation with the Istituto Superiore di Sanità, participation in the World Psychiatric Association's emergency group, support for patients in Ukraine through the Polish Society of Psychiatry, all scientific initiatives and participation at ministerial tables carried out online, and lastly, the preparation of the programme for the National Congress.

We therefore trust that you will come to Genoa in large numbers and that there will be a massive participation of members at the elective assembly on 14 October 2022. Genoa intends to welcome the National Congress with an inauguration that will also include the participation of local celebrities from the world of entertainment in support of a discipline that is always underfunded with respect to both the importance of the pathologies it treats and the number of people affected by them. The opportunity of the NRRP must be appropriately seized in strengthening territorial and outreach services for citizens with the broad involvement of mental health. The number of plenary and symposium speakers is certainly very significant, and we therefore count on the broad participation of members, who have shown a marked interest in the society over the past year, both through the constant renewal of membership fees and the increase in new members, particularly among trainees and new specialists. The serious crisis in the number of specialists in Medicine has also been felt markedly in our discipline. If this trend is confirmed in the coming years, we can expect to have mental health departments with a more adequate number of psychiatrists for their proper functioning by 2026.

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This will allow those who are working under difficult conditions and prevalently on urgency to design care pathways with less pressure. Psychiatry brings about recovery when it succeeds in gaining the consent and co-operation of even the most serious patients. In order to achieve these results, it requires staff who devote time to all aspects of the relationship with the patient and their relatives, and this is achieved if resources, ideas and attractiveness are available. The latter is proper to the discipline that has as its object of study the mind and its functioning, biologically, relationally and socially, which encompasses the essence of the individual and his existence in the world.

Treating mental disorders does not mean treating behaviour that is the result of a number of components on which mental illness can have a more or less important influence. We emphasise this aspect because there is a belief in public opinion that certain behaviours, especially violent or criminal ones, are determined by mental illness and that the perpetrator should be treated rather than serve a sentence. In these situations, it is important to delve into the clinical level and consider the secondary benefits that accrue to the subject if he or she is found to be mentally ill. Every day, those citizens are reported by the police to the Italian Mental Health Centres who, in contact with police officers, have raised doubts about their mental balance. Reporting is appropriate in all those cases where it does not replace other appropriate measures. I am referring to clear violations of the law that are not immediately prosecuted on suspicion of mental illness by the police accompanying to the emergency room a person who has had a mental breakdown for trivial reasons. In these cases, it is imperative that the police protect the health workers by waiting for the outcome of the specialist assessment before not allowing the subject to continue the regular judicial process. The recent abolition of the Judicial Psychiatric Hospitals has shifted the burden of patients with mental disorders to the departments and regions, which far outnumber the residential places in the REMS. In fact, two-thirds of the healthcare response is provided on an outpatient or residential basis by the operators of the Departments of Mental Health, who were already experiencing difficulties in finding specialist doctors.

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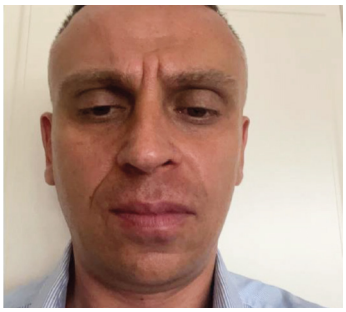
Review



Stefano Barlati

New strategies to improve cognitive symptoms in schizophrenia

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Summary

Cognitive impairment has a key role in schizophrenia outcome: both neurocognitive and social cognitive deficits are related to severe functional disability. As a matter of fact, cognitive deficits seem to explain 20-60% of the variance of everyday functioning. In order to restore cognitive deficits in schizophrenia, different pharmacological and non-pharmacological approaches were developed. Whereas pharmacological interventions include approved treatments and under-study molecules, non-pharmacological interventions include cognitive remediation, non-invasive brain stimulation techniques and physical activity. The aim of the present narrative review is to provide a comprehensive overview of the current available treatments for cognitive impairment in schizophrenia, focusing on pharmacological treatments and cognitive remediation techniques. Our purpose is to increase the knowledge and to understand the principles and methodology of these interventions, also highlighting the evidence of their effectiveness. Findings show that promising results were achieved in this field, but more research is needed to develop specific treatments to improve cognitive symptoms in schizophrenia.

Key words: antipsychotics, cognitive function, cognitive remediation, recovery, schizophrenia, treatment

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Introduction

Cognitive impairment, in past decades, has been consistently reported in patients with schizophrenia. Neurocognitive disability appears early in the course of the disease, even in prodromal phases, and these deficits are widely present in different stages of the illness whether in patients and in their first-degree family members [1]. In 2004, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project has identified seven distinct cognitive domains that are impaired in patients with schizophrenia: speed of processing, attention/vigilance, working memory, verbal and visual learning, reasoning and problem solving and social cognition [2]. Moreover, in the third meeting of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) project, it was cleared that six areas of cognitive domains are damaged in patients with schizophrenia: perception, working memory, attention, executive functions, long-term memory and social cognition [3]. Regarding social cognitive deficits, they include impairments in facial affect recognition, in perceiving and interpreting social cues, in theory of mind (ToM) and in the ability to make appropriate causal attributions for events. Several studies have shown

that both neurocognitive and social cognitive deficits are among the major causes of severe functional disabilities in patients with schizophrenia and they are also related to a worse outcome of the disorder. In a comprehensive literature review, Green et al. [4] underlined that different cognitive deficits might have an impact on specific areas of psychosocial functioning. As a matter of fact, cognitive deficits seem to explain 20-60% of the variance of everyday functioning [5]. A more recent meta-analysis by Halverson et al. [6] explored relationships between functional outcome in schizophrenia spectrum disorders and different domains of neurocognition and social cognition. Overall, this work confirmed associations between social cognition, neurocognition, and functional outcome showing significant small-to-medium effect sizes. Similar associations between neurocognition and social cognition with functional outcome were detected also in the early stages of illness and in first episode patients (FEP). The influence of cognitive reserve as a mediator between cognitive domains and function in FEP was shown by Amoretti et al. [7] and by Gonzalez-Ortega et al. [8]. The influence of cognition on functional outcomes may happen through its influence on functional capacity, the ability to perform critical everyday living skills. Thus, functional capacity may actually be considered as a proxy measure between neurocognition and everyday functioning and it has been found to be quite strongly associated to cognitive performance [9]. Recent studies have shown how cognitive impairment predicts functional outcome even more than positive and negative symptoms and how it is associated with disability in phases of clinical remission too [1,10]. From the greater and detailed knowledge of the role and meaning of cognitive impairment in schizophrenia, its improvement became an essential target in the treatment and in the clinical management of the illness. In order to restore cognitive deficits in schizophrenic patients, there are different pharmacological and non-pharmacological approaches developed. Whereas pharmacological interventions include approved treatments (e.g. antipsychotics and antidepressants) and under-study treatments, non-pharmacological interventions include cognitive remediation, non-invasive brain stimulation techniques and physical activity techniques [11-14].

This review will focus on the analysis of various pharmacological treatments and cognitive remediation techniques, as regards non-pharmacological interventions. We decided to not include other non-pharmacological (eg, aerobic physical exercise) and / or somatic (e.g. brain stimulation) techniques potentially effective, or at least promising, for improving cognitive functioning in schizophrenia. Our aim is to increase the knowledge and understanding of the principles and methodology of these interventions for schizophrenia and to highlight the evidence of effectiveness of such interventions deriving from the current scientific literature.

Pharmacological treatment to improve cognitive functioning in schizophrenia

Cognitive functioning in schizophrenia: focus on treatment management

An important prerequisite for the success of cognitive enhancement interventions in schizophrenia is the stabilization of symptoms through an optimal use of antipsychotics and other psychotropic medications. An ideal pharmacotherapy includes a global assessment, an integrated care plan, and careful attention to therapeutic alliance, in addition to an appropriate choice of the medication(s), adherence, evaluation of comorbidities, and side effects. Avoiding unnecessary or excessive use of medications, as well as reducing the use of drugs with possible negative cognitive effects (for example, anticholinergics), could lead to cognitive benefits [15].

Cognitive functioning in schizophrenia: focus on metabolic profile

The relationship between cognition and the metabolic side effects of antipsychotic medications is complicated. The available literature regarding this topic is sparse, but it suggests a relationship between metabolic comorbidities and worse cognitive function in patients with schizophrenia [16]. Generally, the impact of the metabolic syndrome on cognitive functions is more pronounced in patients with severe negative symptoms. Meta-analyses have further confirmed the effects of metabolic syndrome and type II diabetes mellitus (T2DM) as determinants of poor overall cognition in schizophrenia [17]. Better cognitive performance at baseline has also been associated with a favorable metabolic profile at follow-up in schizophrenia [18]. Individual metabolic syndrome constituent components may exert distinct effects on specific cognitive domains in schizophrenia. For example, a higher waist circumference has been correlated with decreased motor speed and attention/vigilance, while hypertension and elevated triglycerides have been associated with poorer verbal memory. This relationship appears to be very important, considering the increased risk of developing metabolic syndrome in schizophrenic patients.

Cognitive functioning in schizophrenia: focus on first- and second-generation antipsychotics

Treatment with antipsychotics in schizophrenia is often limited to the reduction of positive symptoms, while negative symptoms and cognitive impairment may persist throughout life. First-generation antipsychotics (FGAs), especially, have relatively little influence on cognitive and negative symptoms and may cause adverse side effects, such as extrapyramidal motor symptoms (EPS), tardive dyskinesia, weight gain and sedation. More specifically, FGAs treatment seems to improve certain executive functions on the short period, but there is a decline

relative to baseline of moderate to large effect size (ES) on the long period and, finally, long-term treatment with FGAs can cause cognitive deterioration as a side effect [19]. More specifically, in the randomized NeSSy trial, second-generation antipsychotics (SGAs) presented an advantage over FGAs in cognitive function during medium-term treatment for schizophrenia. Findings also highlighted a distinction between progression to the harmful effects of FGAs with prolonged treatment as opposed to more persistent cognitive benefits with SGAs treatment [19]. This is in line with recent findings from meta-analysis studies on neuroimaging and antipsychotics in schizophrenia patients [20]. SGAs drugs may partially improve cognitive dysfunction, which may be related to their relatively high affinity for serotonin 5HT2A receptors compared with D2 receptors [21]. The apparent cognitive enhancement may be related to one or more of the following effects of atypical antipsychotics agents, not shared by FGAs: increased release of dopamine (DA) and acetylcholine (ACh) in the prefrontal cortex (PFC) and hippocampus; antagonism of 5-HT2A, 5-HT2C or 5-HT6 receptors and stimulation of 5-HT1A receptors. An increased release of DA may particularly lead to stimulation of D1 and D3 receptors, with a possible beneficial effect on cognition, assuming that these receptors are under-stimulated in schizophrenia [22]. An increased release of Ach might lead to enhancement of M1, M4, or α7 nicotinic acid post-synaptic receptors, all of which have been indicated as potentially involved in cognitive impairment in schizophrenia. However, cognitive improvements observed with SGAs may reflect an avoidance of potentially deleterious effects associated with FGAs rather than a specific enhancement of cognition [23]. A meta-analysis by Woodward et al. [24] demonstrated that SGAs improved overall cognitive function to a greater extent than FGAs. McGurk et al. [25] demonstrated a significant improvement in several cognitive domains (selective attention, executive functioning, verbal learning and memory and verbal fluency) in partial responders to FGAs antipsychotics who had been switched to olanzapine. Furthermore, Wang et al. [26] reported that olanzapine could significantly improve short-term memory, immediate memory and memory quotient in first-episode schizophrenic patients. Some findings suggest that aripiprazole may offer advantages over olanzapine in improving neurocognitive function [27]. In an independent systematic review, Houthoofd et al. [28] reported positive effects of risperidone on neurocognitive function in patients with schizophrenia and schizoaffective disorder in processing speed, attention/vigilance, verbal and visual learning and memory and in reasoning and problem-solving. However, the effect of risperidone on social cognition in patients with schizophrenia remains controversial due to conflicting results [29]. Amisulpride seems to improve verbal fluency performance, attention and working memory, with particular benefits on this last one when associated to aripiprazole [30]. Clozapine improves significantly attention and verbal fluency, but only modestly executive functioning and delayed recall [24]. Carpenter et al. [31] reported small advantages of SGAs compared to FGAs in terms of cognitive performance. As shown above, the studies that have focused on the possible differential effects of specific SGAs were not conclusive. In this regard, although a meta-analysis on SGAs effect on cognitive functioning in patients with schizophrenia was able to detect some interesting preliminary results, these were mostly controversial, not showing any uniform effect of each SGAs on cognitive profile [32]. Moreover, a recent meta-analysis on the effect of SGAs subcategories on the cognitive profile of patients with schizophrenia, based upon the chemical structure (the *-pines*, and the *-dones*), showed that the cognitive effect of the two SGAs categories was overall comparable (significant, with a small ES), and there were no clear evidences that the pattern of cognitive effects was different between the two SGAs subtype [33].

On the other hand, given that individual SGAs show different pharmacological profiles and that cognitive function consists of different domains, it is possible that the effects on cognitive function may differ among drugs. This is in line with results from a network meta-analysis study that found SGAs different effects on distinct cognitive domains in schizophrenia patients. In particular, quetiapine, risperidone, and olanzapine had better effects on the overall cognitive profile than amisulpride and haloperidol, but when a single cognitive domain was considered, quetiapine, risperidone and olanzapine were better than amisulpride on executive functions, quetiapine was better than other antipsychotics on attention and processing speed, followed by ziprasidone and olanzapine, and ziprasidone was better than amisulpride and haloperidol on memory [34].

In this perspective, a recent and comprehensive meta-analysis of the effects of antipsychotic treatment on cognitive performance found a favorable effects for amisulpride, quetiapine, lurasidone, olanzapine, perphenazine, risperidone, sertindole, and ziprasidone, with small differences between molecules in different cognitive domains [35]. Inferior effects were observed for remoxipride, clozapine and haloperidol, outperformed by placebo in most cognitive domains, as well as in the composite global cognitive score. Another meta-analysis depicting cognitive effects of SGAs compared to placebo underlined a small significant pro-cognitive for these compounds [36]. Lastly, treatment with antipsychotic medication is associated with moderate improvement in cognitive performance in schizophreniform disorder and in FEP patients [34].

Cognitive functioning in schizophrenia: focus on long-acting injectable (LAI) antipsychotics

Several studies observed an improvement in the cognitive functioning switching from oral formulation of antipsychotics to a long acting injectable (LAI) formulation. For example,

switching from oral risperidone to risperidone LAI (R-LAI) seems to improve verbal memory [37], with a significantly greater mean changes from baseline on the STM-COMET memory scanning test and memory filtering test. Switching from oral risperidone to R-LAI may affect motor processing function and attention improvement efficacy by allowing the dosage of anti-Parkinson's medications (such as biperiden, an anticholinergic drug) to be reduced. The benefits about switching from an oral therapy to a LAI one are also shown in another study, where patients who switched from oral risperidone to paliperidone LAI showed greater improvements in attention and processing speed compared to those who continued on risperidone [38]. As for the oral formulation, second-generation LAI appear to be better on the cognitive profile also if compared to the first-generation LAI. For example, comparing haloperidol decanoate with R-LAI, patients whose therapy was switched to second-generation LAI exhibited significant improvement in memory, executive function, motor processing function, and attention. Also in these cases, a possible explanation could be that FGAs determine EPS more often than SGAs and, for this reason, their use can lead to the coadministration of anti-Parkinson's medications; this association is known to result in cognitive dysfunction [39]. These observations seem confirmed also in the comparison between first-generation LAI and other second-generation LAI: for example, switching to aripiprazole LAI seems to be associated to a better cognitive function in verbal memory, working memory, verbal fluency, and executive function [40]. Different results were found in a more recent meta-analysis that compared oral and LAI formulations of antipsychotics on a wide range of outcomes, such as: efficacy, effectiveness, hospitalizations, adverse events, cognition, functioning and quality of life. In particular, while LAI were found to be superior to oral formulations in terms of risk of hospitalizations and relapse, no significant differences were observed regarding cognitive performance [41].

Cognitive functioning in schizophrenia: focus on antidepressants

In major depressive disorder (MDD), antidepressants are generally associated with beneficial effects on cognitive impairment, which may be mediated at least in part by the improvement obtained in affective symptoms, making it a partially indirect effect. Interventions targeting multiple neurochemical systems simultaneously (e.g. serotonin-norepinephrine reuptake inhibitor, SNRIs, such as duloxetine) might be more likely to improve cognitive performance than treatments targeting only a single system (e.g. selective serotonin reuptake inhibitor, SSRIs, such as escitalopram) [42]. Furthermore, vortioxetine seems to improve cognitive symptoms in MDD through its multimodal action, in particular on different serotoninergic receptors which may modulate glutamatergic neurotransmission [43]. For these reasons, several clinical studies have evaluated the effects of antidepressants on cognitive performance in schizophrenia. In preliminary studies, selective serotonin reuptake inhibitors (SSRIs) seem not to have any effects on cognitive functions, while bupropion, a noradrenaline and dopamine reuptake inhibitor, showed an improvement in attention tests [44]. Moreover, mirtazapine seems to improve visual-spatial ability and general mental speed/attentional control and mianserin added to FGAs showed improvements on memory and learning skills [45]. Unfortunately, a meta-analysis which evaluates the effect of antidepressant augmentation of antipsychotics for the treatment of cognitive deficits in schizophrenia, found no clinically meaningful improvement in any cognitive domain or the composite score [46]. In line with these results, a recent meta-analysis [47], considering the effects of adjunctive fluvoxamine, and a Cochrane Collaboration meta-analysis [48], focused on adjunctive mirtazapine, observed no significant pro-cognitive effect of the antidepressant drug. These findings suggest that, in patients with chronic schizophrenia, cognition does not appear to be significantly improved by the enhancement of serotonergic or noradrenergic neurotransmission on top of antipsychotic. However, antidepressants have been found in some studies to significantly reduce negative symptoms, but also depressive symptoms in schizophrenia patients with a comorbid MDD [49].

Cognitive functioning in schizophrenia: focus on new pharmacological targets

The exact mechanism of cognitive dysfunction in schizophrenia is still debated, but the most supported hypotheses are the glutamatergic, cholinergic, GABAergic, and histaminergic ones [50]. Consequently, a number of GABAergic agents have been studied to stimulate cognition in schizophrenia. Precisely, a dysfunction of γ-aminobutyric acid (GABA) interneurons has been suggested in the pathophysiology of schizophrenia, as the result of a reduction of GABA interneuron density in the frontal cortex and, consequently, an imbalance between excitation and inhibition in the cerebral cortex. According to the "GABA hypofunction" theory, a developmental deficit of inhibitory GABA interneurons may underlie neurodegeneration through an excessive activation of glutamatergic neurons [51]. Moreover, an imbalance between excitatory and inhibitory (E-I) activity, induced by low activity of glutamatergic projections and GABA interneurons in the prefrontal cortex, may lead to impaired working memory in schizophrenia [52]. To correct the "E-I imbalance", new compounds has been developed to treat negative symptoms and cognitive deficits, as the agonists of the glycine site of N-methyl-D-aspartate (NMDA) receptor, DA-D1 receptor, metabotropic glutamate receptor and 5-HT1A receptors [53]. Clinical evidence suggests that serotonin 5-HT1A receptor agonists improve cognitive deficits in schizophrenia, through the correction of the E-I imbalance via the suppression of GABA neural function.

Several compounds have been developed to influence GABA activity, but most of these compounds have failed to demonstrate neurocognitive benefits in large clinical trials [54].

The effects of glutamatergic agents on cognitive deficits have also been investigated. Glutamate is the major excitatory neurotransmitter in the central nervous system and its receptors include NMDA and AMPA receptors. NMDA receptor antagonists, such as ketamine and phencyclidine, can produce clinical and cognitive symptoms of schizophrenia in healthy individuals, leading to the hypothesis that the NMDA receptor could be involved in the pathophysiology of psychosis [55]. Several clinical trials have examined the neurocognitive enhancement benefits of a group of amino acids that act as glutamate agonists by binding to the glycine site on NMDA receptors. These NMDA receptor agonists include glycine, D-cycloserine, and D-serine but none of the currently published studies produced evidence about their benefits on neurocognition: in an initial exploratory study, a single dose of D-cycloserine improved performance on a delayed recall task, but later studies were not able to replicate this finding. Conversely, glycine has shown a beneficial effect as an adjunctive agent to antipsychotics for negative and cognitive symptoms.

Cholinergic agents act on the central cholinergic system, which innervates a diverse range of cortical and subcortical structures, interacting through coordinated acetylcholine (ACh) release with nicotinic and muscarinic receptors. The once common practice of co-administering anti-cholinergic and antimuscarinic agents to schizophrenic patients treated with FGAs to reduce EPS side effects, used to determine a worsening in cognitive impairments [56]. In healthy subjects, the acute administration of anti-muscarinic agents can produce cognitive impairments that mimic the deficits observed in schizophrenic patients [57]. Significant reductions in the expression of M1 and M4 receptors have been consistently reported in the post-mortem brains of schizophrenic patients in regions linked to cognitive function, including the hippocampus, frontal and prefrontal cortex, superior temporal gyrus and the anterior and posterior cingulate cortex. Conversely, the expression of M2 and M3 receptors has been reported as unaltered in the brains of patients with schizophrenia across a number of cortical regions [58]. In accordance with this evidence, it has been suggested that a dysfunctional muscarinic system is contributing to the symptoms of schizophrenia and might represent a therapeutic target. In this regard, clozapine was the first atypical antipsychotic to show nootropic attributes inducing mild improvements across a number of cognitive functions, including learning and memory, eventually attributed to its effects on the muscarinic system [59]. Galantamine is a competitive and reversible cholinesterase inhibitor that also acts as a M1 muscarinic acetylcholine receptor agonist or a modulator of at α4 and α7 nicotinic receptors, and has been used primarily in the treatment of early-stage of vascular dementia and Alzheimer's disease: this drug produced neurocognitive benefits in schizophrenic patients [60]. The five muscarinic receptors share considerable orthosteric binding site homogeneity, while they present a secondary allosteric binding site, which is substantial heterogeneous and became the target for most recently developed drugs. Positive allosteric modulators (PAMs) are a class of allosteric agonists that increase the receptor's affinity for ACh at the orthosteric binding site and consequentially potentiate the receptor's response to Ach. BQCA and PQCA [61,62] are strong, highly selective M1 receptor PAM reported to produce pro-cognitive responses, including enhancing memory function and increasing spontaneous prefrontal brain activity in preclinical trials. In addition to antipsychotic-like qualities, the M4 receptor PAM, VU0467154 and VU1052100 have been reported to enhance cognition [63]. However, more investigations are required to determine the suitability of muscarinic PAMs as new treatments against psychotic and cognitive symptoms in schizophrenia patients.

Development strategies of nicotinic agents mostly focused on the α7-subtype of the nicotinic acetylcholine receptor because of a variety of factors: the genetic links between this subunit and schizophrenia, its high expression rates in key cognitive processing areas (e.g., hippocampus, thalamus, and prefrontal cortex) and the evidence of a decreased expression in post-mortem studies on patients' brains [64]. The α7 nicotinic acetylcholine receptors (α7 receptors) have been shown to play an important role in cognition and have potential therapeutic applications in cognitive impairment in schizophrenia as well as in Alzheimer's disease. Encenicline demonstrated clinically meaningful improvements in cognition and functioning in patients with schizophrenia, whereas varenicline, an α7-subtype of the nicotinic acetylcholine receptor agonist originally approved for smoking cessation, and tropisetron, a 5-HT3 receptor antagonist and α7-subtype of the nicotinic Ach receptor partial agonist approved as antiemetic agent, showed the same inconsistent effects on cognition in schizophrenia [65]. Several cognitive enhancers approved for Alzheimer's Disease, such as antidementia agents (donepezil, rivastigmine, galantamine and memantine), have been tested for their potential to improve cognition in schizophrenia. Unfortunately, cognitive deficits in schizophrenia and in Alzheimer's disease are determined by different mechanisms, as recent findings suggest [66]. Studies on the acetylcholinesterase inhibitors, such as donepezil, rivastigmine and galantamine, gave mixed [67] or negative results [68] in schizophrenia patients. Memantine, usually prescribed as neurocognitive enhancer in Alzheimer's disease, has several mechanisms of action. Although memantine may have possible procognitive effects in schizophrenia patients [69], it does not appear to produce any benefit when added to atypical antipsychotic therapy [70].

Oxytocin is a hypothalamic peptide contributing to maternal infant bonding. Several smaller studies

were done evaluating the effects on social cognitive functioning of this molecule administered intranasally in people with schizophrenia. Further testing is needed to explain whether oxytocin has therapeutic potential for social cognitive deficits and/or negative symptoms in schizophrenic patients [71].

Guanfacine, atomoxetine and reboxetine, three noradrenergic compounds, have been evaluated for their hypothetical procognitive benefits in people with schizophrenia; however, in published clinical trials, all of them have demonstrated a lack of efficacy in this population [72].

Some published studies on serotoninergic agents have evaluated tandospirone, buspirone and ondansetron. However, no study has suggested robust procognitive effects of these compounds [73].

Following the hypothesis that inflammation plays a role in the pathogenesis of schizophrenia, several drugs targeting neuroinflammation and oxidative stress were studied. In fact, increased rates of schizophrenia were observed after infectious events, such as maternal exposure to flu and upper respiratory infections. Studies revealed that in pregnant women, an augmented expression of inflammatory cytokines in the second trimester increased the risk of schizophrenia in their offspring [74]. Viral exposure can reduce the density of receptors relevant for neurocognition, such as D1 receptors in the frontal areas and NMDA receptors in the hippocampus, it can decrease protein kinase B expression and impair axonal integrity [75]. Levels of proinflammatory cytokines, such as interleukin IL-6, are elevated in schizophrenia and have been shown to influence specific brain regions, including prefrontal cortex, medial temporal regions and long-term potentiation in the hippocampus [76]. IL-6 increases oxidative stress, which may interfere with the expression of inhibitory GABA interneurons and impact executive functioning: levels of C-reactive protein (CRP), an inflammatory biomarker, are associated with neurocognitive deficits, but not necessarily with symptom severity in people with schizophrenia [77]. Neuroinflammation indirectly slows neurogenesis, synaptogenesis and dendritic growth as it impacts the activity-dependent transport of brain-derived neurotrophic factor (BDNF), a neuroplasticity-regulating protein. Given their impact on neurocognition, neuroinflammation and oxidative stress are potential targets for psychopharmacological enhancement of neurocognition. Minocycline, a broad-spectrum antibiotic, is a long-acting tetracycline traditionally prescribed as treatment of bacterial infections. There has been recent interest about possible anti-inflammatory, anti-oxidative and neuroprotective benefits of minocycline in people with neurodegenerative disorders and in people with schizophrenia [78]. In this context, also acetylsalicylic acid (aspirin), traditionally used as an analgesic and an antipyretic medication, has gained recent interest as an anti-inflammatory agent in schizophrenia [78]. Particular attention has been paid to the anti-inflammatory properties of simvastatin and rosuvastatin; however, evidences are sparse [79].

Also, interest emerged about the possible pro-cognitive effect of modafinil, a stimulant drug marked as a "wakefulness-promoting medication", that has a yet unclear mechanism of action, but it appears to show therapeutic effects by increasing the expression of histamine in the hypothalamus [80]. Modafinil activates glutamatergic circuits while inhibiting GABA and seems to act as a dopamine agonist, inhibiting the reuptake of dopamine by binding to the dopamine reuptake transporter. In some studies, modafinil was shown to improve attention, memory and executive functioning in people with schizophrenia; however, several studies found no benefits of this agent [81,82].

Omega-3 fatty acids are known to be essential for normal cortical expansion and maturation and functional integrity during prenatal and postnatal phases and during adult development. It has been demonstrated that omega-3 fatty acids may be beneficial to decrease the risk of a frank psychotic disorder in ultra-high-risk individuals, suggesting possible neuroprotective effects [83]. However, very few clinical studies on omega-3 fatty acids have examined their neurocognitive benefits.

Some studies demonstrated that the adjunctive use of N-Acetylcysteine, a precursor of glutathione with antioxidant effects, improves negative symptoms of schizophrenia, and appears to have a neuroprotective effects and to regulate glutamatergic pathways by acting on the redox/glutathione sensitive site of the NMDA receptors, D-serine [84], although there was no direct examination of its neurocognitive benefits [85].

Cannabis sativa is the most widely used drug in the world. It contains over 70 different constituents, including delta-9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD). CBD can interfere with the detrimental actions of Δ9-THC in terms of psychotic proneness and cognitive dysfunction [86]. On the other hand, CBD is a particularly interesting target as a novel approach for cognitive improvement in schizophrenia, in part, due to its strong anti-inflammatory properties. CBD has the potential to limit Δ9THC-induced cognitive impairment and to improve cognitive function in different pathological conditions, but there is limited evidence investigating the therapeutic efficacy of CBD as treatment for cognitive deficits in schizophrenia [87]. However, evidences suggesting cognitive improvement in neurological disorders with CBD treatment emerged [88].

Non-pharmacological interventions to improve cognitive functioning in schizophrenia: focus on cognitive remediation

New non-pharmacological interventions to improve cognitive symptoms in schizophrenia are under study, with the ultimate goal to also obtain a better functional outcome [89]. These interventions, including cognitive

remediation (CR) approaches, are enclosed in a positive light and they are grounded in a recovery rather than deficit model [90]. This new interest is based on the factors associated with an improved quality of life, such as the ability to enjoy social and familial interactions, the advance in educational endeavours and performing well at work. The underlying theoretical framework of these improvements comes from the modern neuroscientific knowledge, which supports the idea that brain would be able of changes and development throughout lifespan [91]. According to this perspective, psychosocial interventions base their theoretical principles on the concept of cerebral plasticity and neurogenesis [13]. As stated by different scientific theories, the development of skills can occur at any age and can help to advance or to restore the brain capacity for improving cognitive and social performance [91]. Learning in an appropriately stimulating environment can help the patient to benefit from brain malleability and to improve functioning [92]. In the next paragraph we will present a definition of CR interventions and their general principles and features. Then we will review the main results reported in recent meta-analyses regarding the efficacy of CR treatments in experimental conditions as well as their effectiveness "in the real world", underlining also the potential neurobiological correlates of the effects of CR in patients with schizophrenia. We will also review current evidence of possible benefits deriving from CR in the early course of schizophrenia and in subjects "at risk" of psychosis.

What is cognitive remediation and how does it work?

One of the first definitions of CR was "the therapeutic process of increasing or improving an individual's capacity to process and use incoming information in order to allow increased functioning in everyday life". This includes methods to train and restore cognitive function and compensatory techniques. More recently, during Cognitive Remediation Experts Workshop (CREW), the definition of CR for schizophrenia became "a behavioural training-based intervention that aims to improve cognitive processes (attention, memory, executive functions, social cognition or metacognition) with the goal of durability and generalization" [93]. According to those experts, "the effectiveness of this training is enhanced when provided in a context (formal or informal) that gives support and opportunity for extending everyday functioning" (Florence, April 2010). As mentioned above, CR bases its theoretical principles on the concept of cerebral plasticity and neurogenesis. Sure enough this intervention, when carried out in a stimulating context, seems to facilitate the development of the brain plasticity [92]. CR strategies can be distinguished into two main models: compensatory and restorative [94]. The treatments based on compensatory strategies try to bypass or to eliminate the specific cognitive deficit, using the subject residual cognitive abilities. On the other hand, the restorative methods use the capacity of the brain to develop and repair itself throughout life-time; these strategies are based on knowledge about neuronal plasticity, working with the aim to correct a specific deficit repairing the specific underlying compromised function. Furthermore, restorative remediation strategies utilize two different approaches: bottom-up or top-down [95]. Bottom-up approaches start with the remediation of basic neurocognitive skills (e.g. attention) and advance to more complex skills (e.g. problem solving). Quite the opposite, top-down approaches use more complex skills with the aim to enhance single and specific neurocognitive domains. Therefore, some restorative strategies take advantage of the use of drill and practice exercises in order to restore cognitive functions and, possibly, to improve neuronal plasticity. On the other hand, other techniques are based on the implementation of new strategies and tend to favour the generalization in different contexts through the execution of different tasks that involve the use of similar strategies [94]. In this context, some CR programs focus on a specific cognitive deficit (e.g. attention or ToM), whereas others work on multiple cognitive domains and are more comprehensive. It is undoubtedly possible that all the above mentioned CR strategies would be complementary and synergic and that the potentiation of specific target functions may favour the development of new compensatory strategies of problem solving, which could be applied and could influence the patient's daily life [96,97]. Structure and frequency of sessions and duration of treatment programs can also vary across the different interventions [98]; CR techniques can be advocated as a package that provides a standard set of exercises or it may be personalized only to target deficits identified in the single individual [99]. To reach the established objectives, CR employs several learning strategies: errorless learning, scaffolding, positive reinforcement, massed practice and information processing strategies [100]. Errorless learning inhibits the implicit encoding of errors, which cannot then be differentiated from correct information by explicit recall. Scaffolding is similar to errorless learning in ensuring a high degree of success for the learner and minimising errors, by carefully regulating the complexity of material to be learnt. The trainee is encouraged to use previously established areas of competence, whilst help is provided with new aspects of learning. Massed practice consists in the practice of a repeated exercise (at least 2-3 times per week) in order to encourage the upkeep and application of the skills developed. Information processing strategies involve verbalization, information reduction, breaking and simplifying the task into smaller steps, providing written prompts, chunking, self-monitoring, mnemonic strategies, categorization, organization and planning. These strategies are otherwise applied to various level in different methods of CR, depending on whether they are primarily based on repeated execution of specific tasks or on the implementation of new strategies. A few factors have influence on a positive treatment response for CR training, such as training of the therapist, motivation of the patient,

type and intensity of training and cognitive resources at baseline [96]. In past decades, a number of CR techniques have been developed and adopted in multimodal treatment approaches in schizophrenia: computerized and non-computerized, designed for individual or group settings. The main structured protocols of cognitive training for schizophrenia are described in Table I. At the same time, many authors investigated the efficacy on CR in patients with schizophrenia. In the next paragraph we will analyse the principal results about this topic.

Cognitive remediation: focus on social and non-social cognition

Starting from the definition of CR, we know that one of the aims of these behavioural training-based interventions is to improve cognitive processes, that are recognized as the most important predictors of functional outcome and quality of life in people with schizophrenia [112]. Various published meta-analyses support the efficacy of CR for enhancing cognitive outcomes. Nevertheless, the first results that we can find from the literature are controversial. In two independents reviews, Kurtz et al. [113] and Twamley et al. [114] underlined that CR programmes have effective components that hold promise for improving cognitive performance (with a medium or large ES). On the other hand Pilling et al. [115], in a first review based on few studies, reported that CR had no benefit on attention, verbal memory, visual memory, planning, cognitive flexibility or mental state and concluded that CR did not appear to confer reliable benefits for patients with schizophrenia and could not be recommended for clinical practice. After the earliest reviews, it was developed a rich body of literature that well established that CR is effective in reducing cognitive deficits with long-term benefits in schizophrenia [113,114,116,117]. All these reviews find a moderate ES of CR programmes in improving neurocognitive deficit. The results about cognition acquire robustness when CR is associated with psychiatric rehabilitation: this combination led to significant favourable outcomes for global cognition [118]. One of the most important meta-analyses of the available controlled studies of CR in schizophrenia performed by Wykes et al. [117] including 40 studies and about 2.000 patients, showed a moderate improvement in overall cognitive performance (more effective when patients were clinically stable). Authors declare that no treatment element (remediation approach, duration, computer use, etc.) was associated with cognitive outcome. This work underlined some durability of the effects (ES = 0.43), as shown in follow-up studies [119]. Durability of effects were also underlined in two recent studies performed by Buonocore et al. [120,121], who found out that all cognitive abilities improved with CR, in association with standard rehabilitation, remained stable over time from the end of treatment to evaluation at 5 and 10 years, except for psychomotor speed and coordination that showed a significant decrease. Positive effects of CR on global cognition were found also in a recent metanalytic work, indicating that CR improves cognition across several domains including processing speed, working memory and learning, much more in inpatient settings [122]. Overall, the most recent and comprehensive meta-analysis on the effectiveness of CR for people living with schizophrenia included 130 studies and a total of 8,851 participants, and found a consistent small-to-moderate positive effect of CR on cognitive performance and functioning [11]. Regarding the instrument utilized to administer CR, computer-assisted cognitive remediation (CACR) methods [123] showed significantly improvement especially on the domains of attention and working memory (marginally on other neurocognitive domains). Moreover, a recent meta-analytic study performed by Kambeitz-Ilankovic et al. [124] underlined that the effects of CR on cognitive outcomes are consistently reported both for training administered in a computerized fashion and for training supplemented by human guidance (SHG). Nonetheless, the comparison between CR administered with or without human guidance revealed that the human approach gives largest effects on the cognitive subdomains of working and verbal memory. On the other hand, no difference was reported between individual and group method.

A substantial but controversial body of literature was presented also for social cognition, starting from the first meta-analysis that debates this topic, performed by Grynszpan et al. [125], highlighting the efficacy of CACR particularly in social cognition and ending with some specific reviews that analyse promising results of training specifically developed for social cognition in schizophrenia. As example, a meta-analysis performed by Kurtz and Richardson [126] stressed the greatest effect of social cognitive treatments on facial affect recognition (FAR), with a moderate-to-large ES for affect identification and a large ES for affect discrimination. Authors also reported a moderate ES for ToM and a large impact on measures of observer-rated community and institutional functioning. According to Yeh et al. [127], that more recently conduct a meta-analytic work on CACR and social cognition with particular attention regarding ToM, there are different recent results around this topic. Prikken et al. in fact [123] found no effect of CACR on social cognition, whereas Lindenmayer et al. [128] suggested that CACR could enhance social cognition. Authors highlight that findings are inconsistent also regarding the relationship between ToM deficits and cognitive load in schizophrenia [129]. Hence, they focused their analysis on CACR and ToM in schizophrenia, founding that computerize training did not significantly enhance affective ToM ($p = 0.42$), instead treatments without computerized training were significantly superior in terms of improving cognitive ToM.

Concerning all different methods of interventions (CACR and pen and pencil), two recent systematic reviews [130,131] highlight positive results, emphasizing that targeted interventions produce more significant improvements, particularly in the domains of affect recognition, emotion processing and ToM. Results were less clear for social

Table I. The main structured cognitive remediation protocols in schizophrenia.

Cognitive Training	Target	Duration	Setting (Individual/ Group)	Computer assisted/Not computer assisted	Restorative/ Compensatory	Top-down	Bottom-up	Drill and practice	Strategy Coaching	Individual adjustment
IPT [101]	Cognitive functions, social skills and problem solving	Sessions of 60 minutes, 2-3 times a week (about 12 months)	Group (6-8)	Not computer assisted	Restorative	+	+	+	+	-
NET [102] (Bell et al., 2001)	Cognitive functions and social cognition	Sessions of 45 minutes at least 5 times a week (about 6 months)	Individual/Group	Computer assisted sessions and not computer assisted sessions	Restorative	-	+	+	-	+
NEAR [103]	Cognitive functions and problem solving	Sessions of 60 minutes, twice a week (about 4 months)	Individual/Group (3-10)	Computer assisted sessions and not computer assisted sessions	Restorative	+	-	-	+	+
CRT [97]	Cognitive functions	40 sessions at least 3 times a week, 45-60 minutes each one	Individual	Not computer assisted session	Restorative	+	+	+	+	+
CET [104]	Cognitive functions and social cognition	Biweekly sessions (about 2,5 hours every week) for 24 months	Group (couples and then groups of 3-4 couples)	Computer assisted sessions and not computer assisted sessions	Restorative	+	+	+	+	-
INT [105]	Cognitive functions and social cognition	30 biweekly sessions, 90 minutes each one	Group (6-8)	Computer assisted sessions and not computer assisted sessions	Restorative	+	+	+	+	-
SSANIT [106]	Cognitive functions, social cognition and social skills	NT: biweekly sessions of 1 hour SST: weekly sessions of 2 hours Duration: 6 months	Individual (Group)	NT sessions: computer assisted SST sessions: not computer assisted	Restorative	+	+	+	+	+
TAR [107]	Social cognition	12 sessions twice a week, 45 minutes each one	Small groups of two patients and a psychotherapist	Computer assisted sessions and not computer assisted sessions	Restorative/ compensatory	-	+	+	+	+
SCIT [108]	Social cognition	24 weekly sessions, 50 minutes each one (about 6 months)	Group (6-8)	Computer assisted sessions and not computer assisted group sessions	Restorative	-	+	+	+	-
SCET [68]	Social cognition, ToM	36 sessions of 90 minutes, twice a week (about 6 months)	Group	Not computer assisted	Restorative	-	+	+	+	-
SCST [109]	Social cognition	12 weekly sessions, 60 minutes each one (about 3 months)	Group (6 patients)	Computer assisted sessions and not computer assisted group sessions	Restorative	-	+	+	+	-
Cogpack*	Cognitive functions	Sessions variables in duration and frequency (starting from 2-3 weeks)	Individual	Computer assisted	Restorative	-	+	+	-	+
CIRCUITS [110]	Cognitive functions and metacognition	12 sessions, three times a week, 60 minutes each one (40 sessions)	Individual	Web-based computerised CR therapy with therapist plus independent session	Restorative	+	+	+	+	+
CCT [111]	Cognitve functions	12 two hour- weekly sessions (about 3 months)	Group (4-8 patients)	Group sessions with two facilitators	Compensatory	+	+	+	+	-

CCT: compensatory cognitive training; CET: cognitive enhancement therapy; CRT: cognitive remediation therapy; INT: integrated neurocognitive therapy; IPT: integrated psychological therapy; MCT: metacognitive training; NEAR: neuropsychological educational approach to remediation; NET: neurocognitive enhancement therapy; NT: neurocognitive training; SCET: social cognition enhancement training; SCIT: social cognition and interaction training; SCST: social cognitive skills training; SSANIT: social skills and neurocognitive individualized training; SST: social skills training; TAR: training of affect recognition; ToM: theory of mind.
** Cogpack (www.markersoftware.com) is a typical computer-assisted cognitive remediation (CACR) technique.*

perception, a complex construct that tends to be culturally specific [132], and for attributional bias, domains that appear to be more difficult to measure and train. Such skill in 'cognitive restructuring' is thus more challenging for people with schizophrenia to acquire, compared to emotion perception training which comprises drills and practice to achieve implicit learning and automation [133].

Promising results were found also in a recent meta-analysis performed by Nijman et al. [134] that investigate the efficacy and the durability of different types of social cognition training, with an analysis of moderators of treatment outcome. Authors found that broad-based social cognition training significantly improved emotion perception, social perception, ToM and social functioning. Targeted social cognition training had the largest effect on emotion perception and social perception. These improvements were maintained at follow-up but were generally less than at post-treatment. Regarding treatment variables that significantly moderated outcome, they underlined that individual treatments were more effective for emotion perception, but group treatments worked better to improve social functioning.

In recent years, studies about CR pay their attention on a better understanding of whom is able to benefit from CR: this knowledge would enable clinicians to more effectively refer patients to CR or tailor the intervention to the individual [135]. In particular, the identification of CR response predictors in patients with schizophrenia is still a topic with equivocal findings and only a few studies have looked for the relationship between CR response or resistance and the biological, socio-demographic, clinical, and cognitive features in schizophrenia [136]. In a recent review of literature, Barlati et al. identify some type of predictors, underlining that CR seems to be more effective in schizophrenia patients with the following features: younger age, shorter duration of illness, few disorganized symptoms, greater pre-treatment cognitive reserve, greater improvement after CR and lower dosages antipsychotics in their current treatment. About CR characteristics, a much larger effect of CR on functioning

was found out when a strategic approach was adopted and when CR was offered as part of broader psychosocial rehabilitation interventions. On the other hand, international scientific literature is controversial on the following predictive factors: genetic variability, cognitive and functional impairment at baseline [136]. Moreover, Seccomandi et al. [137] performed a systematic review of the putative factors which may affect CR response, with the aim to identify potential individual factors at baseline, moderators, that may predict treatment outcomes and that may be used to tailor CR and improve its benefits. Authors highlighted five categories of moderators that might influence CR response: demographics, biological, cognitive and functional, psychological and illness-related characteristics. Nonetheless, they underline that there was no high-quality replicated evidence, which identifies reliable moderators of CR response. Recently Vita et collegues, in their meta-analisys, focused on ingredients of effectiveness, moderators of response, as well as barriers and facilitators for implementation in real-world clinical practice of rehabilitation services represent fundamental issues that require further discussion and investigation. No difference in effectiveness was observed regarding pencil-and-paper or computer-delivered interventions, or regarding individual- or group-based programs. On the contrary, the active participation of a trained therapist, the repetition of cognitive exercises, the development of novel cognitive strategies and the presence of activities to facilitate transfers of cognitive gains in the real-world context emerged as core elements of effectiveness [11]. Moreover, factors that have a positive effect on efficacy have also been shown to positively influence treatment acceptability [138].

The growing amount of data on CR refers mostly to adult and chronic patients with schizophrenia, but less it is known about the effectiveness of CR in the early course of the disease and its possible application on the prodromal phase of the illness [139]. Early phases of the illness are considered a crucial period that could potentially influence its course and during which neural plasticity is thought to play a major pathoplastic role [140]. This could justify the theoretical usefulness of interventions targeting cognitive improvement [141]. Revell et al. [142] in their meta-analysis on CR in early schizophrenia underlined that CR in FEP had a positive effect on global cognition; the areas with major results are verbal learning, memory and social cognition (although only in 3 of trials). Improvements nearing uncorrected significance were also seen in processing speed, working memory and in reasoning and problem solving. These results were similar to that reported in the Wykes et al. [117] meta-analysis performed on "chronic" patients, although the ES in FEP review are smaller. The work of Revell et al. [142] reported in conclusion of meta-analytic estimate that CR had a non-significant positive effect on global cognition. Nonetheless, this preliminary non-significant effect, according to Lewandowski [143], underlines that CR is feasible and potentially efficacious in recent-onset and high-risk patients. This recent review highlights that, in recent-onset patients with schizophrenia, most reports show improvements after CR in one or more domains of cognition. With regard to people at high risk of developing psychosis, some studies report similar promising results although findings on efficacy are inconclusive due to small sample sizes and lack of control [144]. Some studies indicate that effects of CR in these populations may be of similar or greater magnitude as those seen in chronic patients [140], suggesting that young patients with greater potential for plasticity may indeed benefit as much or more than patients with presumably reduced plasticity.

In a recent review, Bellani et al. [145] pay their attention on CR-induced structural and functional brain changes in early SCZ. According to the authors, current literature showed a protective effect of CR on some regions of grey matter volume, as in selected medial-temporal (i.e. hippocampus, parahippocampus and amygdala) and thalamic regions. Functional changes acted on dorsolateral prefrontal and insular cortices both associated with improvements in cognitive performance and emotion regulation. Authors conclude that CR appears to be a promising treatment in the approach of cognitive impairment and neural alterations associated with the early phase of schizophrenia, but future research are needed to clarify whether the positive effects of cognitive training persist over time. Overall, preliminary evidence supports the extension of CR in early course and high-risk populations.

Finally, while recent evidence suggest that CR interventions can also be delivered remotely [146], attrition rates appear to be very high, and more research is currently needed to confirm its effectiveness in this format: in-person treatment sessions currently represent the optimal standard [147].

Cognitive remediation: focus on psychosocial functioning

In past decades different outcome measures were recognized as being relevant for effective interventions in schizophrenia such as: quality of life (QoL), obtaining and working competitive jobs, family and quality of and satisfaction with interpersonal relationships, leisure time and other elements of daily living, finances, the ability to solve interpersonal problems and physical and mental health [148]. Some of these key elements compose psychosocial functioning – defined as patients' ability to fulfil their role in society as a member of a family or in a professional career – that should be a priority target for therapeutic interventions in schizophrenia [148]. As we know starting from scientific literature [149], functional outcome is strongly influenced by cognitive impairment. According to some authors, cognitive deficits explain 20-60% of the variance of real-life functioning. Since these premises, it is crucial that CR could generalize its results and could have impact on social functioning of patients. Starting from McGurk et al. meta-analysis [150], that includes 26 studies

(about 1,500 patients), CR programmes demonstrate a small/medium ES for functioning (ES, 0.35). Moreover, CR programs that provided adjunctive psychiatric rehabilitation had significantly stronger effects on improving functional outcomes (ES, 0.47) than programs that did not (ES, 0.05). McGurk et al. found that CR intervention, that included strategy coaching, had stronger effects on functioning than programs that focused only on drill and practice technique. According to the authors, this effect is accordant with previous researches showing that cognitive impairment reduces response to psychiatric rehabilitation [151] and suggests that improved cognitive performance may empower some patients to benefit more from rehabilitation. Also in a previous meta-analysis on CR in schizophrenia, Twamley et al. [114] underlined that all the different types of approaches, whether computer assisted or not, have effective components that are promising for improving everyday functioning. Similar results were found at a later time in Wykes et al. meta-analysis [117], in which CR was associated with a small/medium ES for functioning (ES, 0.35) with a significant heterogeneity in the ES. Stronger ES for improved psychosocial functioning were found by authors in studies that provided adjunctive psychiatric rehabilitation and use of drill and practice plus strategy coaching (ES, 0.62), compared to drill and practice only. This moderator of response could justify the significant heterogeneity in the ES. These findings are also in line with the results of a meta-analysis of integrated psychological therapy (IPT) [101], in which the strongest effects on functioning were found in programs that integrated CR and social skills training rather than programs that provided either intervention alone [116,152].

Furthermore, in 2019 Van Duin et colleagues performed a meta-analysis in order to investigate whether a combination of psychiatric rehabilitation (PR) and CR reinforces the effect of a stand-alone PR or CR intervention on separate domains of functioning. They analysed three areas: vocational, social and community functioning. Regarding vocational functioning, the combination of CR and PR led to significant favourable outcomes for employment rate, hours worked, job duration and quality of performance in work or education compared with a single PR intervention. Similar results were found in social functioning, in which the combination of CR and PR had significant favourable outcomes for social skills if compared with a single PR intervention. Quite the opposite, no significant beneficial effects were found in community functioning (independent and daily-living skills, role adjustment and performance and social and occupational functioning) when it was compared with a single PR intervention. Results on social and work outcomes were confirmed also by Kambeitz-Ilankovic et al. [124] that found a small, significant effect of CR on functional outcomes. Also the more recent and comprenshive meta-analisys carried-out by Vita et al. [11] underline that the integration of CR into a structured psychiatric rehabilitation program or its association with other evidence-based psychosocial interventions produced better improvements in both cognition and functioning.

With respect to the persistence of the effects on daily functioning, patients treated with the 6 months CRT showed a significant decrease in functional performance after 5 years, compared to the end of treatment. On the contrary, no differences between the end of CR intervention and 5 years later were observed within group that received further standard rehabilitation for a year [120]. Finally, a study performed by the same research group confirmed that functional improvement of cognitive remediation interventions together with standard rehabilitation interventions is still conserved 10 years after the end of the treatments [121].

Results on functioning were controversial regarding meta-analyses focused only on CACR methods, that seem to be effective in some areas of functioning. On one hand, according to Prikken et al. [123], in patients receiving computerized cognitive drill and practice training compared to a control condition, significant effects on global functional outcomes were absent. On the other, Chan et al. [153], who performed a review on CACR and productivity outcomes, found that CACR can enhance productivity outcomes for patients with severe mental illness (SMI), including higher employment rate, longer duration of work and higher income, improving also quality of life in this population.

Examining results derived from social cognitive training (SCT), we can observe that the first systematic review, that debates this topic [131], concludes that there is also a need for more studies to measure intervention effects on real-world social functioning and that there is potential in including learning strategies (i.e errorless learning) and harnessing technology (i.e virtual reality and home-based online training) in order to improve distal outcomes of social competence and social functioning. More promising results derive from following studies: Grant et al. [154] found a positive effect on functional outcomes used both broad-based and focused studies. The majority of included studies which found an improvement in functioning also reported an improvement in ToM and in social perception. These data support the idea that improvement in ToM may benefit more directly functional outcomes [155], because ToM seems to be relevant in everyday social interactions [156] and because social perception requires the ability to decode social interactions that is strongly associated with functioning improvement. Also, Nijman et al. [134] found that broad-based SCT (with and without CRT) had a significantly larger effect on social functioning, that persists at follow-up. In this meta-analysis the group treatment was the only variable that significantly moderated outcome. Concerning CR in in-patients, a recent meta-analysis of Cella et al. [122] showed that there was a positive but no statistically significant effect in favour of CR compared to treatment as usual (TAU) or TAU plus additional interventions. Authors supposed that assessing social and vocational outcomes in in-patient settings may be

difficult because patients may have limited opportunities to practice and take part in activities assessed as part of functional assessment measures.
Significant positive effects of CR were seen on functioning also in FEP [142], with a significantly larger effect in treatments, which employed CR with adjunctive psychiatric rehabilitation (e.g. psychoeducation and training to develop social, vocational and daily living skills), replicating the findings of the Wykes et al. meta-analysis performed on adult / chronic patients. These results could indicate that targeting cognitive impairments early in the course of the disorder can result not only in cognitive improvement per se, but also in significant functional benefits in such critical domains as employment, social functioning, and major role functioning [8,139]. In addition, the results could include CR as part of continuing rehabilitation, that may be able to translate cognitive gains directly to better function.

Cognitive remediation: focus on clinical symptoms

Some small but encouraging results, that infer by CR techniques, were found also in schizophrenia symptoms: as we know from scientific literature, there is a better prognosis in individuals with psychosis, in terms of functioning and symptoms remission, for those with better cognitive performance [157]. Recently it become established the idea that CR has a direct effect on symptoms. Since the first meta-analytic study performed on this topic [114], CR (both computer-assisted and not) demonstrated its positive effects on symptoms, with the unknown possibility if these effects were sustainable. Also, two meaningful meta-analytic works agreed with these preliminary results, finding a small significant ES for symptoms, that however disappeared at follow-up assessment [117]. A more recent work conducted by Kambeitz-Ilankovic et al. [124], underlines similar effects, finding a small, significant ES of CR on clinical outcomes, particularly in two subdomains: negative and depressive/anxious symptoms. The same results were found in a meta-analysis about CACR training [123], with some small differences: CACR methods showed small/moderate, but only marginally significant effects on negative symptoms and total symptoms, whereas the analysis including all CR methods shows no significant effects on positive, general, and total symptoms, nor on clinical global scores. According to Wykes et al. [117], also Kambeitz-Ilankovic et al. [124] showed no differential response between human guidance of treatment and computerized CR. These results suggest that computerized training programmes, that have the potential to be performed independently by patients, are effective [123]. Regarding integrated interventions (for example, IPT), whether they yielded some significant immediate and long-term effects in more proximal outcomes, small effects were found in symptoms [116]. Similar, significant positive effects of CR were seen also in FEP patients on global symptoms: in more detail, CR had a significantly smaller effect on symptoms both when it was delivered one to one with a therapist, as well as when it was delivered in groups [142].
Other specific trainings, for example social cognitive training programmes do not report significant effects on positive and negative symptoms of schizophrenia [126]. According to the authors, the limited effects of social cognitive training on positive and negative symptoms may reflect the multi-determined nature of these disease domains, including emotionally charged family relationships. These interventions produced moderate size effects on general symptoms, suggesting that social cognitive training may be more effective in influencing general psychiatric symptoms such as depression and anxiety.
Furthermore, some studies gave specific attention on CR effect on negative symptoms [158]. Authors underline that negative symptoms are not traditionally considered a primary target for CR, but their results demonstrate a small to moderate effect of CR on negative symptoms at post-therapy, with this effect being maintained at follow-up. These findings highlight that CR may have similar ES to other available pharmacological and behavioural interventions designed to tackle negative symptoms directly [159]. Authors suggest that future researches should explore in detail the relationship between cognitive and negative symptoms in schizophrenia. This suggestion was conducted in a recent study exploring the effect of integrated neurocognitive treatment (INT) on relapse rates, which were significantly lower in the INT condition compared with TAU both during therapy and at one-year follow-up. This analysis points out that the relapse rate after therapy was associated with significant reductions in negative and general symptoms, improvements in functional outcome and overall cognition. Authors underline that out of these variables, negative symptoms were identified to show the strongest association with relapses after therapy [160].

Conclusions and future directions

Cognition in schizophrenia is an important target of intervention due to its relationship to outcomes and recovery. In patients with schizophrenia, both social and non-social cognitive deficits are related to outcomes and can limit recovery even when other support has been provided [93]. Different pharmacological and non-pharmacological approaches were developed to restore these deficits, although these interventions are still under study and discussed. Some of these treatments, such as SGAs and CR, demonstrate their efficacy also through neuroimaging studies, that underline their neurobiological effects [20,161]. Furthermore, for each intervention we know that some individuals show little benefit and other much more. This difference leads to an increasing interest in investigating potential moderators, mediators and predictors of treatment, with the aim to make each treatment tailored for each patient. Despite there are still some future perspective to observe, different studies support

the idea that an integrated approach is required in order to increase everyday functioning and to decrease disability in schizophrenia [89]. To sum up, as recently pointed out by expert group consensus on cognition in schizophrenia [162], pharmacological and non-pharmacological approaches moderate both functional improvements and recovery.

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Original article

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Analysis of prescribing patterns in patients treated with long-acting antipsychotics in a Department of Mental Health: VIRAL project

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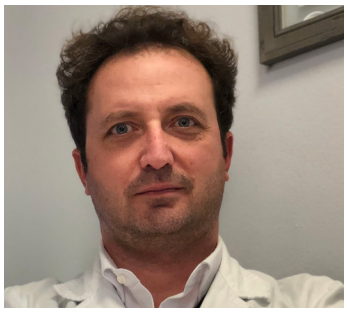

Salvatore Calò

Summary

Objectives. Despite poor adherence to antipsychotic medication leading to multiple relapse in patients with schizophrenia, LAI formulations of antipsychotic drugs remain an underutilized options. The purpose of this study is to analyze the prescription pattern of antipsychotic long acting in a department of mental health of Italy to allow clinicians to identify specificifiers for the different drugs use.

Methods. We used the electronic data from Mental Health Information System of the Puglia Region, Italy, and health care utilization from the Health Information System of the Puglia Region, Italy, to analyze 995 subjects with age ≥ 18 years and who received at least one administration of one of AP-LAI. The study was approved by the Ethics Committee of the Local Agency of Health of Lecce (VIRAL). We divided the total sample (995 subjects) in two groups: Second Generation Antipsychotics Long acting, (SGAs-L, n = 447) and First Generation Antipsychotics Long acting (FGAs-L, n = 548). We evaluated different clinical and demographic variables such as sex, age, main diagnosis, disease duration, presence of medical comorbidities, substance and/or alcohol problems.

Results. Our results showed an use of SGAs-L in younger people (age, 45.19 ± 11.69) with lower duration on illness (52.58 ± 12.25 ys) and with higher prevalence of substance and/or alcohol problems (15.2%). FGAs-L remained a more utilized option in the older patients (age, 52.58 ± 12.25 ys) in particular with schizophrenia (75.9%) or psychotic disorder otherwise specified (7,5%). The prescription pattern showed a specific indication for some SGAs-L: Aripiprazole for young (age, 40.29 ± 10.69), different diagnosis than schizophrenia (52.7%) women (57.0%), Paliperidone for young (age, 46.55 ± 11.83) schizophrenic (69.2%) man (67.6%) with high relative prevalence of medical comorbidity (15.9%), Olanzapine for patients with relative higher substance and/or alcohol problems (19.7%).

Conclusions. Age, sex, diagnosis and other clinical conditions can guide clinicians to use AP-LAI in different patients.

Key words: LAI antipsychotics, schizophrenia and related psychotic disorders, second generation antipsychotics, first generation antipsychotics, drug utilization

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Conflict of interest
The Authors declare no conflict of interest.

Introduction

Long acting injectable antipsychotics (AP-LAI) have always been one of the main therapeutic strategies in patients suffering from psychotic disorders with poor compliance with treatments. Adherence in subjects with schizophrenia is extremely low, with discontinuation rates of 74% in the first 18 months from the start of treatment [1,2] and, in subjects with the first episode, 42% at one year regardless of the treatment used, second or first generation antipsychotics [3]. The consequences of this condition are devastating with relapse rates in patients with the first episode, exceed 70% in the first 5 years [4].

The benefits of continued antipsychotic treatment for relapse prevention are well-known, such as reduction of risk of structural brain damage, treatment resistance and maintenance of social functioning [5,6]. The achievement of symptomatic remission for a period of at least 3 months in the first 2-5 years of the disease, defined as the critical period [6,7], is predictive for good personal and social functioning in the medium and long term [8].

Despite these evidence, long-acting antipsychotics continue to be an under-used option [8] with percentages of use varying on average between 10% and 25% [9,10]. The low percentage of use could lie in several factors including: a) the presence of non-univocal results deriving from the comparative studies with the relative oral formulations b) the absence of specific criteria that can guide the clinician in the choice of an LAI treatment [8-10]. The data from naturalistic studies show a significant advantage in favor of LAI antipsychotics over oral formulations in terms of reduction of the risk of relapses [11], on the other hand the data from randomized clinical trials (RCTs) do not always support this evidence [12].

The differences in these results could be linked with characteristics of the studies themselves. In controlled trials, the exclusion of subjects with usually considered associated with a high rate of non-adherence for the presence of medical comorbidities or substance abuse, would lead to not bringing out a clear difference between the different formulations. On the contrary, the inclusion of these subjects in naturalistic studies would bring an evident advantage in favor of LAI antipsychotics [13,14].

The absence of specific criteria could be barrier prevent their widespread adoption and the clinicians see this formulation reserved for patients with a long history of disease or relapses [8,15]. For the same reasons many clinicians believe that AP-LAIs should not be used until patients experience multiple relapses, are chronically ill, and/or overtly demonstrate nonadherence [16-19].

The objective of our study was to detect specific characteristics of use relative to the different long-acting antipsychotics of both first and second generation by analyzing the prescriptions of these drugs in a real-world setting.

Materials and methods

Study design

We conducted an observational, retrospective study in which all patients from the Mental Health Centers of the Mental Health Department of Lecce (13 centers for a general population of about 800,000 inhabitants on an area of 2,759 km^2) treated with AP-LAI from January, 1, 2016 to December, 31, 2017 (2 years), were enrolled.

The inclusion criteria were: a) age ≥ 18 years; b) at least one administration of one AP-LAI. The AP-LAI evaluated in this study were: fluphenazine decanoate (FLU), haloperidol decanoate (HAL), zuclopenthixol decanoate (ZUC), risperidone RP (RIS), olanzapine pamoate (OLZ), one month paliperidone palmitate (PP1), three month paliperidone palmitate (PP3), aripiprazole monohydrate (ARI). The observation nature of the study in a real-world setting did not provide for specific exclusion criteria (Fig. 1).

Prescription data were then linked, using civil registration numbers, to information on psychiatric diagnoses from the main data source of Mental Health Information System of the Puglia Region, Italy [20] and to information on health care utilization from the Health Information System of the Puglia Region, Italy [21].

The study, Valutation of Impact and Representation of Antipsychotics Long acting (VIRAL), program no. 108, was approved by the Ethics Committee of the Local Agency of Health of Lecce (Act 27, December, 13, 2018). All subjects included in the analysis signed regular informed consent for the use of their data in aggregate form for research purposes. This is an observational, retrospective study, it did not entail any additional risk to patients nor did it affect new prescriptions of any medication.

Sample and variables

The total sample (995 subjects) was divided in two groups according the class of AP-LAI: Second Generation Antipsychotics, (SGAs-L, n = 447), First Generation Antipsychotics (FGAs-L, n = 548) (Fig. 1). The main clinical-demographic characteristics were assessed: sex, age, main diagnosis, disease duration, presence of medical comorbidities, substance and/or alcohol problems. The medical comorbidities (n = 140, 14.17%) were: diabetes mellitus (n = 23), hypertension (n = 34), neurological disease (n = 15), thyroid dysfunction (n = 13), obesity (n = 11), metabolic syndrome (n = 17), hepatitis (n = 15), HIV (n = 2), Cancer (n = 3), kidney disease (n = 2), lung disease (n = 5).

The diagnoses were made according to the criteria of the ICD-9 CM: schizophrenia (ICD-9-CM codes 295.0-295.9), bipolar disorder and related disorders (ICD-9-CM codes 296.4-296.9), depressive disorders (ICD-9-CM code 296.3), personality disorders (ICD-9-CM codes 301.0-301.9) and psychotic disorder otherwise specified,

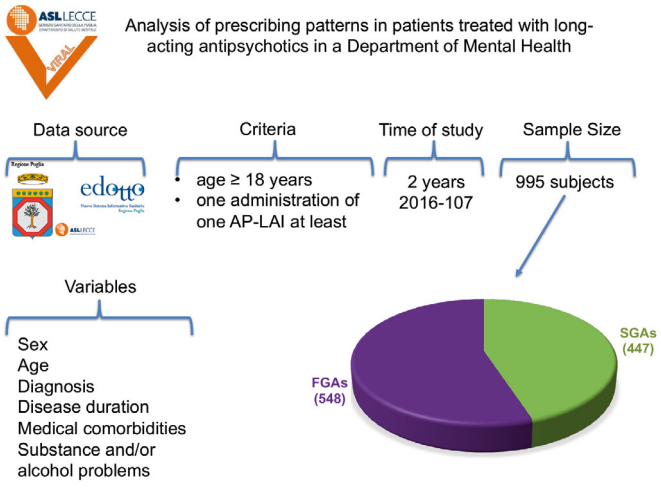


Figure 1.
Study design and sample size.

including dementia and other chronic psychotic conditions, (ICD-9-CM codes 294.0-294.9).

Statistical analysis

Sociodemographic and clinical characteristics of patients, were described by means of descriptive analysis, using means and standard deviations (SD) for continuous variables and percentages for categorical variables.
We analyzed the differences in the two groups about clinical and demographic variables examinate in the study. Then we evaluated the difference between the single drugs to define a prescribing pattern.
We used Pearson Chi-square (χ^2) test we analyzed the difference between the two groups or drugs on gender, diagnosis, presence of medical comorbidity and substance or alcol related problems.
Furthermore, the comparison between relevant estimates was carried out by means of Student's t-test for unpaired data or by means of binomial and one-way Anova tests. All tests were performed at a significance level of 0.05 (two-tailed). Statistical analysis will be carried out using statistical software (SPSS version 23).

Results

SGAs-L vs FGAs-L

We enrolled a sample of 995 subjects with an average age of 49.27 years [12,55] and with a higher prevalence of subjects of male sex (M/F = 61.51/38.49%). When we analyzed the differences between the two groups (SGAs-L *vs* FGAs-L), the difference between male and female subjects was greater in the FGAs-L group (M/F = 63.1/36.9%) than in SGAs-L group (59.5/40.5%) although not statistically significant (NS, p > 0.05) (Tab. I).
The mean age (SGAs-L *vs* FGAs-L; 45.19 ys *vs* 52.58 ys) as well as the duration of disease (SGAs-L *vs* FGAs-L; 10.85 *vs* 17.96) were statistically (p < 0.0001) lower in the SGAs-L group than in FGAs-L group (Tab. I). The difference between the two groups for both parameters was on average about 7 years.
The diagnosis of schizophrenia (FGAs-L *vs* SGAs, 75.9 *vs* 64.4%) and psychotic disorder otherwise specified (FGAs-L *vs* SGAs-L, 7.5 *vs* 3.4%) were statistically (p = 0.0001) more frequent in the FGAs-L group (Tab. I). On the contrary, in the group treated with SGAs-L, the diagnosis of bipolar disorder (SGAs-L vs FGAs-L, 28,2% vs 10,6%) was more frequent than in FGAs-L group (Tab. I). There were no differences (NS, p > 0.05) between the two groups for the other diagnoses (depressive disorder and personality disorder).
The presence of medical comorbidities was not different (p > 0.05) in the two groups (SGAs-L *vs* FGAs-L, 14.32 *vs* 13.87%) (Tab. I).
The present of substances and/or alcohol problems was more frequent in the SGAs-L group, in a statistically

Table I. Sociodemographic and clinical characteristics of patients between the two groups (SGAs-L vs FGAs-L).

Variables		SGAs-L (447)	FGAs-L (548)	p
M/F, n (%)		266/181 (59.5%/40.5%)	346/202 (63.1%/36.9)	0.242*
Age, mean ± SD (years)		45.19 ± 11.69	52.58 ± 12.25	0.0001**
Duration of disease, mean ± SD (years)		10.85 ± 8.66[a]	17.96 ± 10.28[b]	0.0001**
Diagnosis, n (%)	Schizophrenia	288 (64.4%)	416 (75.9%)	0.0001**
	Bipolar disorder	126 (28.2%)	58 (10.6%)	0.0001**
	Depressive disorder	5 (1.1%)	13 (2.4%)	NS*
	Personality disorder	13 (2.9%)	20 (3.6%)	NS*
	Unspecified psychotic manifestations	15 (3.4%)	41 (7.5%)	0.0001**
Medical comorbidity, n (%)		64 (14.32%)	76 (13.87%)	NS*
Substance and/or alchol problems, n (%)		68 (15.2%)	53 (9.7)	0.008*

*a: 12 subjects missing data; b: 7 subjects missing data; *Pearson χ^2 test; ** Student's t-test; NS = p >0.05.*

Table II. Prescribing pattern of single APs-LAI.

	M, n (%)	F, n (%)	SCZ, n (%)	Other diagnosis, n (%)	Medical comorbidity, n (%)	Substance or alchol problems, n (%)
HAL (371)	228 (61.5)	143 (38.5)	295 (79.5)	76 (20.5)	55 (14.8)	32 (8.6)
FLU (154)	106 (68.8)	48 (31.2)	110 (71.4)	44 (28.6)	16 (10.4)	20 (13.0)
ZUC (23)	12 (52.2)	11 (47.8)	11 (47.8)	12 (52.2)	5 (21.7)	1 (4.3)
ARI (93)	40 (43.0)	53 (57.0)	44 (47.3)	49 (52.7)	10 (11.8)	15 (16.1)
OLZ (71)	38 (53.5)	33 (46.5)	57 (80.3)	14 (19.7)	5 (7.0)	14 (19.7)
RP (95)	61 (64.2)	34 (35.8)	56 (58.9)	39 (41.1)	19 (20.6)	13 (13.7)
PP1 (185)	125 (67.6)	60 (32.4)	128 (69.2)	57 (30.8)	29 (15.9)	26 (14.1)
PP3 (3)	2 (66.7)	1 (33.3)	3 (100)	0 (0)	1 (33.3)	0 (0)

significant manner (p = 0.008), than in the FGAs-L group (SGAs *vs* FGAs, 15.2 *vs* 9.7%) (Tab. I).

Prescribing patterns

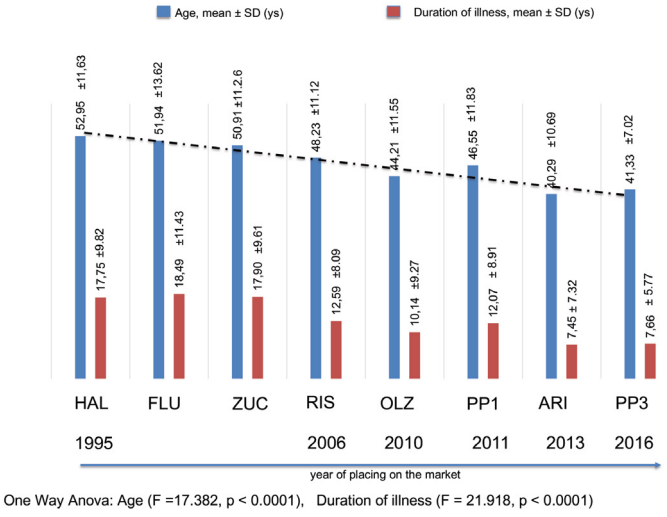
Treatment with Haloperidol decanoate (n = 371) was the main treatment prescribed among the FGAs-L group (67.7%), followed by fluphenazine decanoate (n = 154, 28.1%) and zuclopentixol decanoate (n = 23, 4.2%) (Tab. II). Within the SGAs-L group, the main treatment prescribed was Paliperidone palmitate 1 month (n = 185, 41.4%) followed by Risperidone RP (n = 95, 21.3%), Aripiprazole monohydrate (n = 93, 20.8%) and Olanzapine pamoate (n = 71, 15.9%) (Tab. II). Treatment with Paliperidone palmitate 3 month resulted in only 3 subjects (0.6%), probably conditioned by the recent marketing with respect to the observation period of the study (2016-2017).

The analysis of the clinical-demographic characteristics would seem to highlight a certain attitude of the clinicians to use specific drugs, the statistical significance found for variables such as sex, diagnosis (schizophrenia vs all other diagnosis), the presence of medical comorbidities and substance or alcohol problem, as well as age and disease duration could configure specific prescribing patterns (Tab. II, Figs. 2, 3).

Haloperidol decanoate was more prescribed in absolute terms (n = 317), in subjects affected by schizophrenia (79,5%), male sex (61.5%) and with higher age (52.95 ± 11.63) and duration of illness (17.75 ± 9.82), with more frequent medical problems (14.8%).

Fluphenazine decanoate was widely used in subjects suffering from schizophrenia (71.4%), of male sex (68.8%) and with relative higher age (51.94 ± 13.62) and duration of illness (18.49 ± 11.43) than SGAs-L group. The medical problems was less frequent in this group of patients (10.4%).

Zuclopentixol decanoate didn't present a particular use in terms of diagnosis and sex, although, as with other drugs of the same class, the subjects have a higher age (50.91 ± 11.26) and duration of disease (17.90 ± 9.61) than



One Way Anova: Age (F =17.382, p < 0.0001), Duration of illness (F = 21.918, p < 0.0001)

Figure 2.
Age and duration of illness analysis for the single AP-LAI.

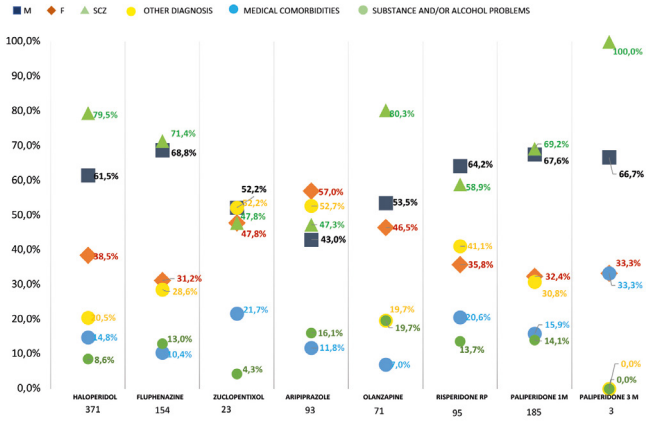


Figure 3.
Prescribing patterns of APs-LAI.

SGAs-L group. The presence of medical comorbidities would seem particularly high (21.7%).
Aripiprazole monohydrate had slightly higher prescription in female subjects (57.0%), unique than the other AP-LAI, without particular differences based on the diagnosis (SCZ *vs* Other D., 47.3 *vs* 52.7%) and with a relatively lower age (40.29 ± 10.69) and duration of illness (7.45 ± 7.32) than other AP-LAI. The present of medical comorbidities was comparable to the other AP-LAI (11.8%).
Olanzapine pamoate was more prescribed in subjects with schizophrenia (80.3%) without differences about gender (M/F, 53.5/46.5%) with a lower age (42.21 ± 11.55) and duration of illness (10.14 ± 9.27) than the FGAs-L and with statistically significant lower medical comorbidity than other AP-LAI (7.0%). On the contrary, the presence of substances and/or alcohol problems were more frequent than other AP-LAI (19.7%).
Risperidone RP was prescribed more frequent in subjects with schizophrenia (58.9%), male sex (64.2%), as FGAs-L. The age (48.23 ± 11.12) and duration of illness (12.59 ± 8.09) were lower than FGAs-L but higher than other SGAs-L with the exception of Paliperidone one month. The medical comorbidities (20.6%) and the substances and/or alcohol problems (13.7%) were present with a high frequency.
Paliperidone one month had a greater use in subjects suffering from schizophrenia (69.2%), male sex (67.6%), like the FGAs-L drugs. The age (46.55 ± 11.83) and duration of the disease (12.07 ± 8.91) were lower than the FGAs-L group but higher than the other SGAs-L. The medical comorbidities (15.9%) and substances and/or alcohol problems (14.1%) were more frequent than in other APs-LAI.
The small number of subjects treated with Paliperidone 3 month (n = 3) didn't allow an analysis of its use.

Discussion and Conclusions

Long-term pharmacological therapy can play an important role in enhancing adherence, preventing relapse, and in encouraging successful rehabilitation and re-entry into society in patients with schizophrenia [22]. The possibility to assuring continuity of treatment represent a clinical priority within the treatment plan. The development and introduction of long-acting antipsychotic treatments has been a turning point in the treatment of schizophrenia where poor adherence to antipsychotic medication leading to a need for multiple rehospitalizations and a substantial direct and indirect cost burden [23].
For several years the only present of first generation antipsychotic in long acting formulation, due to the burden of high risk of extrapyramidal side effects, has limited clinicians to be reserved this formulation only in the most extreme cases both in terms of severity and chronicity of the disease. In the last 15 years, despite the introduction of second-generation antipsychotics in long-acting formulation, reducing the likelihood of disabling side effects, the attitude of clinician would not seem to have changed [15]. Some recent evidence supports the benefits of early intervention with APs-LAI [24] but LAI antipsychotics remain an underutilized treatment option. The lack of specific indications probably represents a limit to their wider use in clinical practice.
The data of our study confirm this latter evidence by finding a shorter age and duration of illness in subjects treated with SGAs-L than in subjects treated with FGAs-L. The use of APs-LAI for indications different from schizophrenia could reflect the attitude of clinicians about the use of their oral formulations. In particular SGAs-L would seem more used for bipolar disorder while FGAs-L for psychotic disorder other specified, including dementia and other chronic psychotic conditions.
The most prescribed drugs were Haloperidol in the FGAs-L group and Paliperidone in the SGAs-L group. This finding could derive from the greater ductility of these two drugs given by the presence of a wider range in the dosage of the long acting formulations as well as by the characteristics of the sample itself constituted in the majority by subjects suffering from schizophrenia.
In general, our data confirm the use of SGAs-L in younger subjects and with a lower duration of disease, in particular for the certain drugs with a most favorable side effects' profile. Aripiprazole was more used in female subjects. Both data (age and sex) could be explained by the lower tendency of Aripiprazole to induce alterations in prolactin levels and in general sexual functioning. These side effects, particularly important for young subjects in terms of non-adherence to treatments, would seem to induce the clinician to make greater use of this molecule in this subgroup of subjects.
The SGAs-L, compared to the FGAs drugs, present a greater use in bipolar disorder; this could recall the indications present in the technical data sheet of the related oral formulations. In confirmation of this, among the various drugs belonging to the SGAs class, there was a greater use of Aripiprazole in bipolar disorder, and a greater use in schizophrenia for Paliperidone and Risperidone.
With regard to the use of substances and or alcohol, if the data reveal on the one hand a class effect with a greater use of SGAs drugs, on the other hand a specific effect for single molecule is not detected.
On the contrary, with regard to medical comorbidities, mostly cardio-metabolic, where there is no class effect (SGAs *vs* FGAs), among the second generation drugs a greater use of Risperidone and Paliperidone was found compared to Olanzapine, burdened by its greater metabolic side effect.
The naturalistic design of this analysis certainly represents a limit in the possibility of interpreting the results obtained in a more specific way. At the same time the absence of specific exclusion criteria describes the use of APs-LAI in a real-world setting.
In conclusion, our study highlights how the differences

profile in terms of indications and safety of the different APs-LAI, obviously also affect the clinician's choice of the type of long-acting antipsychotics used with increased use of SGAs-L in general in younger patients, in particular Aripiprazole for young female with different diagnosis than schizophrenia (bipolar disorder), Paliperidone for male schizophrenic patient with medical comorbidity and Olanzapine for patients with relative higher substance and/or alcohol problems.

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Original article

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Perinatal mental health in ASL Roma 1: preliminary data from SaMeP, a specific pathway for healthcare in pregnancy and postpartum

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Summary

Objectives. Perinatal depression can involve up to 1 woman over 5 and it is one of the most frequent causes of early maternal death. As a large number of depressed women still remains unidentified, international guidelines underline the importance of early screening procedures and suggest the building of dedicated pathways of care within the public health service. The objective of this article is to present the organization of SaMeP and report preliminary data relating to 2021.

Methods. First-tier (Whooley questions) and second-tier screening (EPDS and SaMeP semi-structured interview) was administered to a large sample of women in ASL Roma 1 family clinics and birth centers. The semi-structured interview gives a specific attention to the occurrence of traumatic events and to their impact on the emergence of psychopathological aspects.

Results. 611 women received first-tier screening and among them, 116 women (18.9%) were referred to second-tier screening. 24 women (3.9%) were then referred for specialistic consultation with SaMeP psychiatrists. This last sample was divided into two groups based on the presence or absence of a traumatic history. When compared to the group without a traumatic history, the group exposed to trauma scored higher in EPDS ($p < 0.001$) and "SaMeP 2" pathway, that offers a higher level of care, was more frequently activated ($p < 0.015$).

Conclusions. The availability of SaMeP, a specific pathway for healthcare during pregnancy and postpartum, involving a systematic screening procedure for a wide group of women made it possible to intercept a large number of conditions worthy of clinical study (18.9% of the population involved). History of trauma is confirmed as an index of psychopathological severity during perinatal period.

Keywords: depression, pregnancy, postpartum, screening, psychological trauma

Introduction

Perinatal mental health

Becoming a mother implies a biological, psychological and social challenge. Perinatal psychiatric disorders represent a real clinical emergency. As a matter of fact, perinatal depression can involve up to 1 woman over 5 and is one of the most frequent causes of early maternal death [1,2]. When we talk about perinatal

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mental health we do not refer only to the mother, but to the whole family triad: paternal perinatal depression can affect up to 9% of fathers [3,4].
Moreover, epidemiological studies confirmed the association between perinatal psychiatric disorders and fetal and neonatal outcomes, suggesting that the exposure to environmental factors in womb or during the very first weeks of life can induce a different epigenetic expression of DNA, hesitating in a modified susceptibility to developing chronic diseases in adult life. Children exposed to different kinds of abuse have a higher risk of developing social, emotional and behavioral issues in adolescence, such as anxiety, depression and hyperactivity [5-8]. Child maltreatment is a solid predictive factor of psychiatric disorders in life span [9] and it is associated also to an early onset, more chances of comorbidity, more severe symptoms, and resistance to pharmacological treatment.
Many international scientific societies developed guidelines on how to manage perinatal psychiatric disorders, underlining the importance of early screening procedures during pregnancy and postpartum and suggesting the institution of dedicated pathways of care, made by networks of professionals [10,11].
However, a large number of women still does not receive the correct information about mental health issues and available treatment in pregnancy and postpartum. The lack of those information dramatically interferes with early diagnosis and intervention. ASL Roma 1 recognized this unmet need and implemented a multidisciplinary pathway of care, creating a professional network where different services are involved in caring for women affected by perinatal mental health issues and for their children.

Perinatal mental health in ASL Roma 1: SaMeP

The Local Health Trust "ASL Roma1" in Rome, provides healthcare to 6 out of the 15 Councils (Municipi) in which the city of Rome is divided (i.e., Municipio 1, 2, 3, 13, 14, and 15), serving more than 1 million inhabitants. Female population aged between 16 and 50 is of approximately 231.000 women. In 2021, a total of 2024 pregnant women had access in the 12 Family Clinic of the ASL Roma1 and a total of 1,465 women gave birth at Santo Spirito Hospital and San Filippo Neri Hospital birth centers.
Over the last two years ASL Roma 1 created the "Percorso intervento per la Salute Mentale Perinatale (SaMeP)", a specific pathway for perinatal mental health. SaMeP has the goal of creating a network between actual health services who have a role in assisting women affected by mental health issues in preconception, pregnancy and postpartum, up to 12 months after delivery.
SaMeP pathway involves a screening phase for risk factors, specialistic consultation and the construction of a targeted therapeutic intervention.
SaMeP psychiatrists work in multidisciplinary groups formed by other professional figures from different services: midwives, psychologists and social workers from family clinics, midwives, psychologists and ob-gyn from hospital settings and psychologists, nurses and social workers from mental health settings. To avoid stigma and to strengthen the family clinic role in our multidisciplinary intervention, psychiatric specialistic consultation is delivered inside the patient's family clinic. The SaMeP psychiatrist will stratify the risk, differentiating low, moderate and high-risk clinical cases with the goal of defining and starting the most adequate intervention for that specific patient.

Clinical intervention pathways: SaMeP 1, 2 and 3

Three SaMeP pathways have been defined, differentiating one to the other depending on intensity of care (Fig. 1).
SaMeP 1: (low risk). SaMeP psychiatrist will consult and monitor patients at their family clinic, along with family clinic psychologist.
SaMeP 2: (moderate risk). SaMeP psychiatrist will either refer the patient to the proper Community Mental Health Team (Centro di Salute Mentale, CSM), if the patient is not known, or give a specific consultation to the already existing mental health equipe. In those cases it is important to identify a case manager, to structure specific interventions and to define, within the 32nd week of pregnancy, a peripartum management plan.
SaMeP 3: (high risk). In case of a psychiatric emergency (e.g. postpartum psychosis), SaMeP psychiatrist will refer the patient to the Emergency Room and will activate an urgent psychiatric consult to evaluate admission to Psychiatric Intensive Care Unit.

"Linea nascita a rischio"

"Linea Nascita a Rischio" is a specific pathway addressed to children born in difficult situations, which include maternal mental health issues. This pathway has been developed by the Children and Adolescents Mental Health Service (Tutela Salute Mentale e Riabilitazione dell'Età Evolutiva - TSMREE) and it has the goal of early detection and treatment of neurodevelopmental issues. Women can be assessed with their newborns and partners by the "Linea Nascita a Rischio" team within the 3rd month after birth.

Materials and Methods

Whooley questions

They are a set of two yes/no questions originally developed in 1994 as a tool for General Practitioners to diagnose depression and a few years later implemented as an early test to diagnose perinatal depression in women. Nowadays the Whooley questions are administered in many countries all over the world, during midwives consultations [12].

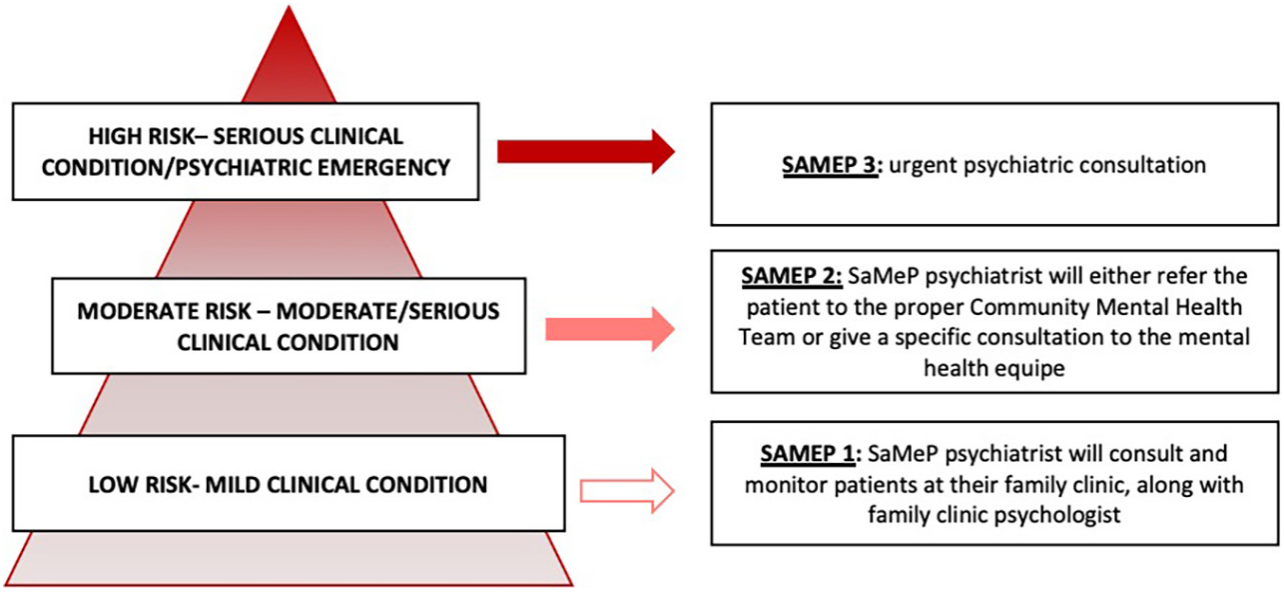

Figure 1.
SaMeP 1, 2 and 3, different pathways of care.

Edimburgh Postnatal Depression Scale (EPDS)

The EPDS was developed in 1987 with the goal of creating a test for depression that adequately explored specific symptoms in the perinatal period and that could be completed by women themselves [13]. EPDS is internationally used both in antenatal and postnatal care. It is composed by 10 items scored 0 to 3.

SaMeP 2 semi-structured interview

A semi-structured interview has been developed by SaMeP psychiatrists, and it is administered by family clinic and hospital psychologists in second-tier screening. The semi-structured interview explores risk factors for developing mental health issues in pregnancy and postpartum. Sociodemographic data, information about pregnancy and delivery, personal and family history for psychiatric disorders are collected. Consistent with literature [14,15], a specific attention is given to traumatic events and to their impact on the emergence of psychopathological aspects. The following types of trauma have been evaluated: traumatic birth, physical or psychological trauma, loss and separation, history of neglect or child maltreatment.

First-tier screening

Midwives, psychologists or pediatricians in Family Clinics and Birth Centres administer the Whooley Questions [12] as suggested by NICE Guidelines ad other International Guidelines on perinatal mental health [10]. This evaluation can be repeated many times in the perinatal period, during birth and breastfeeding classes, prehospitalization right before delivery, 3rd day postpartum, 7th day postpartum (first pediatric assessment) and 40th day postpartum (ob-gyn consultation).

Second-tier screening

Once a patient answers positively to one or both Whooley questions, she goes through the second-tier screening procedure by meeting a clinical psychologist, either in hospital or family clinic setting. This screening involves the administration EPDS and a semi-structured interview. When the patient tests positive in one or more evaluations, she is referred for the SaMeP psychiatric consult. The SaMeP psychiatrist evaluates whether the patient needs to be monitored or whether she needs psychiatric pharmacological treatment that is compatible with pregnancy and breastfeeding. Also, they evaluate whether the patient needs to be taken under the care of Community Mental Health Team (CSM).

Results

In 2021, 611 women received first-tier screening. Among them 496 women (81.2%) answered “NO” to both Whooley Questions, 115 women (18.8%) answered “YES” to at least one of the questions, resulting positive to first-tier screening. 116 women (18.9%) were referred to second-tier screening (Fig. 2). One of the women was referred to second-tier screening despite resulting negative to the Whooley Questions, as a consequence of a clinical evaluation.
24 women (3.9%) were referred for specialistic consultation and followed up by SaMeP psychiatrists (Fig. 2).

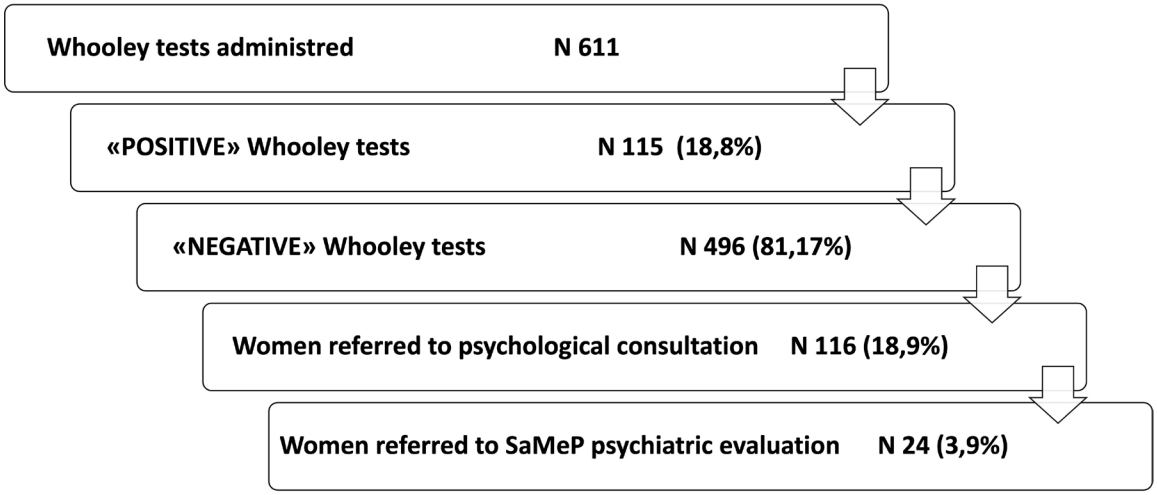

Figure 2.
Asl Roma 1 SaMeP first and second-tier screening in 2021.

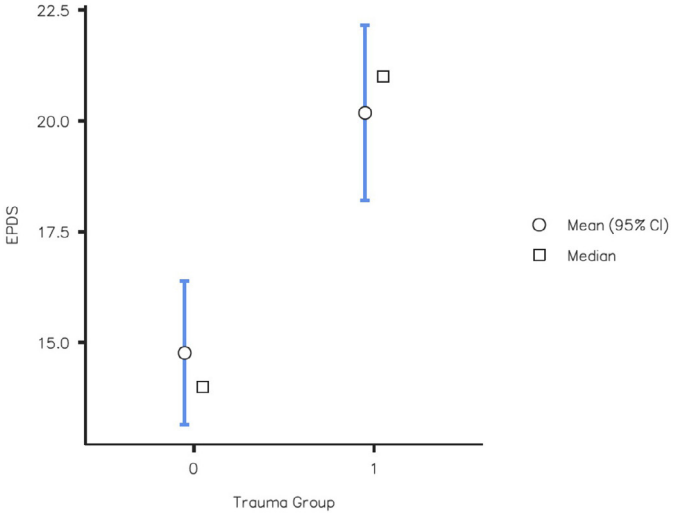

Figure 3.
Mean EPDS scores of each group. Group 1 has been exposed to trauma, while Group 0 has not a traumatic history.

The women evaluated and followed up in SaMeP pathway were an average of 34.21 years old; 70.8% (17) were italian nationals, whereas foreigners came mainly from Georgia, Bangladesh, Romania, Nicaragua, Perù, Czech Republic. 29.2% (N 7) had a university degree or higher, 37.5% (N 9) had a high school diploma and 33.3% (N 8) had a lower degree, such as middle school diploma or less; 70.8% (N 17) was employed, 29.2% (N 7) was unemployed; N 8 women (33.3%) were pregnant when referred, whereas 16 women (66.6%) were in their postpartum period.
All evaluated women had a stable partner and only 8% (N 2) described their relationship as unstable. However, only 29.2% described themselves as well supported socially and within their families; 50% (N 12) of SaMeP sample felt that they were poorly supported and 12.5% (N 3) stated that they didn't have any kind of social support. 2 women did not answer the question.
In terms of their pregnancy, while 18 women (75%) reported their pregnancy to be normal, 6 women (25%) reported different medical issues in pregnancy. Moreover, 14 women (58.3%) had previous pregnancies; 8 women (33.3%) had a history of previous miscarriages, 3 of them had more than one; 5 women (20,8%) of the sample fell pregnant through *in vitro* fertilization treatment.
In terms of psychiatric history, 1 woman was already followed up by the Mental Health Department, but 9 women (37.5%) were positive for previous psychiatric history. 2 women (8.3%) had a previous admission in a psychiatric ward. 5 women (20.8%) were positive for psychiatric family history. 11 over 24 women (45.8%) had a positive history of trauma. In 6 cases (25%) trauma was referred to loss or separation. 4 women (16.6%) experienced child maltreatment.
The average EPDS result was 17.25 (DS 4,04).
For 7 cases (29.1%) the "SaMeP 2" pathway was activated, with referral to the Community Mental Health team (CSM), "SaMeP 1" was activated for the remaining cases, with joint monitoring between family clinic and SaMeP psychiatrist. No case was referred to "SaMeP 3" in 2021.
Despite every woman evaluated by SaMeP psychiatrists was referred to "Linea Nascita a Rischio", only 2 of them accepted.
The sample of women evaluated with SaMeP psychiatric counseling was divided into two groups based on the presence or absence of a traumatic history. The group exposed to trauma scored higher in EPDS (20.2 ± 3.34) than the group without a traumatic history (14.8 ± 2,98), with a statistically significant extent ($t = -4.20$, $p < 0.001$) (Fig. 3). Consistently, our results show that, for the group

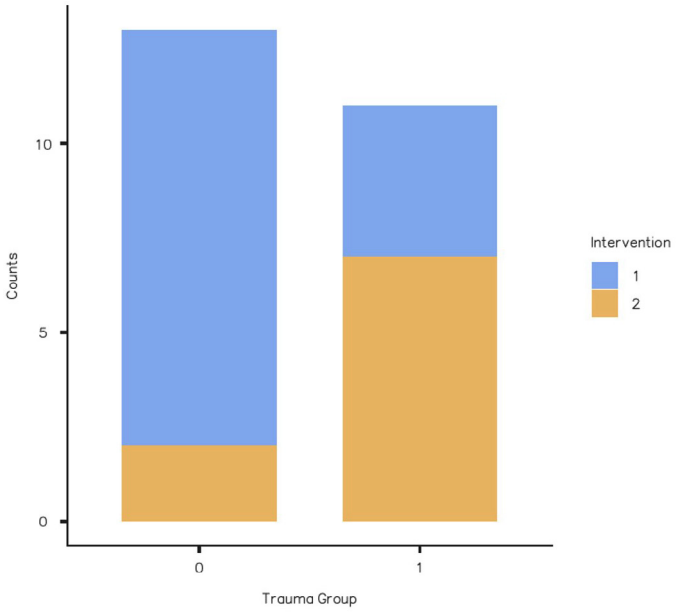

Figure 4.
Differences in SaMeP pathway of care between Group 0 (no traumatic history) and Group 1 (exposed to trauma).

with a history of trauma, "SaMeP 2" pathway, that offers a higher level of care, was more frequently activated than for the group without a traumatic history (χ^2 5.92, $p < 0.015$) (Fig. 4). The two groups did not differ for the other variables.

Discussion and Conclusions

In this article we presented the organization of SaMeP and reported preliminary data relating to 2021. Over the year considered, more than 600 women underwent first-tier screening. The activation of the screening procedure within a large group of women has made it possible to intercept any condition worthy of clinical study.

It is important to provide a systematic screening procedure on perinatal psychopathology within the public health service, as perinatal depression is still an underdiagnosed pathology. The most alarming data indicate that a large number of depressed women still remains unidentified [16-18].

In line with what is described in major international guidelines, we believe that Whooley questions are particularly suitable as first-tier screening. This tool can, in fact, be administered with extreme ease and, for this reason, it can be perfectly integrated into the usual clinical practice [12].

There are different reasons that explain why it is unrealistic that women affected by perinatal mental issues, ask for help autonomously and spontaneously. Relevant matters are the high perception of stigma and self-stigma, together with a dramatic poverty of information on perinatal psychopathology and the widespread unrealistic beliefs about motherhood and the way in which women should deal with it [19,20]. Also, the depressive symptomatology itself can determine a substantial obstacle to the request for support, since women with perinatal psychiatric pathology frequently report feelings of guilt or failure [21,22].

In our sample, a total of 116 women (18.9%) was considered worthy of clinical study and underwent second-tier screening through psychological interview and test evaluation. Within this group, only 24 women were referred to the psychiatrist.

This reflects literature data, which state that while 1 in 5 women (about 20% of all pregnant or postpartum women) experiences a perinatal mental disorder, approximately 5 out of 100 women receive a diagnosis of severe perinatal mental disorder [1,23]. It is extremely important to be able to intercept this portion of population as perinatal depression, besides having significant consequences for the entire family, means for the child a concrete increase in the risk of developing psychiatric pathologies in adolescence and adulthood [24]. In the last twenty years, depressive pathology has again been conceptualized as an inflammatory pathology, calling into question the dysregulation of inflammatory indexes such as PCR, IL-6, IL1 beta, TNF alfa, IFN beta [25].

In this regard, interesting data show that an effect of this inflammatory dysregulation on neurodevelopment can be found in children of women affected [26,27].

Furthermore, some authors have highlighted how, in children of women suffering from perinatal depression, a persistent alteration of immunological parameters can be found in adulthood, independently from the occurrence of life-time depressive episodes [27].

Current research strongly highlight the clinical need to focus more and more attention on the effects that a current psychopathological condition may have on future generations. For this reason, we value our involvement with TSMREE (Child and Adolescence Mental Health Team) because taking care of the mother is associated with a specialistic follow up of the child up to 24 months after birth [28,29]. We consider it crucial, to continue in raising awareness on perinatal mental health also to allow progressively a greater adhesion of families to the dedicated pathways of care: only 2 women in our sample accepted to be referred to "Linea nascita a rischio" and we believe that this has a link with the perception of stigma connected to perinatal psychopathology.

Interestingly, in our study, almost half of the patients referred to the psychiatrist had a history of trauma, confirming the relevance of the traumatic experience as an index of psychopathological severity.

According to literature, women who suffered trauma in childhood, especially sexual abuse, loss or illness of a loved one, are more vulnerable to developing perinatal depression, and the risk of disease increases four-fold if three or more traumatic events occurred lifetime [30,31].

Although the most frequent form of violence in pregnancy

is emotional abuse, physical violence is also particularly represented. In pregnancy, violence implies a more complex meaning, threatening the physical integrity of the mother and the unborn child: having suffered from physical or sexual violence during pregnancy can not only cause a depressive disorder, but can also compromise the future parenting function of mothers [32].

WHO data report that between 1 and 28% of women suffers sexual abuse perpetrated by the partner during pregnancy. Physical violence suffered during pregnancy is often described as direct attacks on the mother's belly, with specific harmful intentions [33,34]. Other studies have clearly reported an increased risk of depression in women who experienced loss or separation from a loved one during perinatal period [35] and in line with this, the 25% of the group of women referred to psychiatric consultation, reported having experienced loss or separation.

Furthermore, the 16.6% of the sample referred to the psychiatrist, reported an history of child maltreatment, which is widely considered a solid predictor of psychiatric disorders at different ages of life [9] and is associated not only with the onset of mental health problems, but also with an early age of onset, with a higher rate of comorbidity, a greater severity of symptoms and resistance to drug treatment.

Our perspectives for the future are to increase the culture of perinatal mental health in all professionals involved in women's care through education; moreover, we have new partnerships coming up, that will help building our net of professionals.

Currently, the absence of specific data on the subthreshold sample is a limit of the study, but a more systematic data collection also including the patients who tested negative at the first and/or second-tier screening is already underway, with the objective of increasingly focus on prevention and identification of risk factors.

New perspectives

Two partnerships have been launched, the first with CRARL (Alcohol Reference Center of the Lazio Region, ASL Roma 1, Department of Mental Health) involves screening for early recognition of alcohol consumption during pregnancy and a multidisciplinary care plan involving CRARL, Family Clinics and SaMeP for comorbidities with mental health problems. The second partnership, with LUMSA University (Libera Università Maria Santissima Assunta), provides the administration of an implemented screening procedure addressed to all mothers and fathers participating to birth classes in Family Clinics during their 3rd trimester of pregnancy. The parental couple is monitored up to 24 months after birth and a home visiting intervention within the postpartum period is foreseen.

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Original article

Role of the pharmaceutical form in the development of addiction from psychoactive substances

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Summary

Introduction. In the development of addiction and abuse of psychoactive substances, both factors related to the person, of a psychopathological and metabolic type, and factors related to the substance come into play and, in the latter case, the 3 most important are the half-life, the potency pharmacodynamics and pharmaceutical form. In this article we want to focus on the description of how this last characteristic is important in facilitating or not conducts of abuse both relating to therapeutic substances such as opioids and benzodiazepines and to illicit substances.

Materials and methods. The article was performed according to the PRISMA guidelines, where the characteristics of the studies eligible for the review included being related to the thematic of addiction, regarding mainly related to pharmacokinetics, dynamics and pharmaceutical form. ccStudies were identified by searching papers according to their relevance via PubMed/MEDLINE. Finally 38 studies and one book were suitable for the inclusion in this review.

Discussion and conclusions. In recent years, the market for psychoactive substances has undergone changes with the introduction, for the purpose of dealing, of both legitimate substances such as psychotropic drugs and new psychoactive substances, which are added to the old substances already present. The pharmaceutical form and its absorption, also linked to the route of administration, are fundamental in modulating the activity of the compounds taken and pharmaceutical forms with rapid absorption and prompt release are more often involved in drug addiction behaviors. This should be borne in mind above all in relation to the prescriptions of some classes of psychotropic drugs and especially if they are protracted for a long time in those that are more easily additive.

key words: addiction, psychotropic drugs, pharmacology, formulations, pharmaceutical chemistry

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Introduction

Substance use disorder (SUD) is a condition in which the excessive use of one or more substances leads to clinically significant impairment or distress and effects that are harmful to physical and mental health or to the welfare of other individuals [1]. The disorder is characterized by a pattern of pathological

continued use of a drug, which results in adverse social consequences related to drug use, such as failure to meet work, family or school obligations, interpersonal conflicts, or problems legal [2]. There are ongoing debates regarding the exact distinction between "substance abuse" and "substance addiction"; in DSM-5, substance use disorder replaced and unified the previous categories of DSM-IV: substance abuse and addiction. the data on the use of psychotropic substances are relevant: According to estimates, in the European Union about 83 million adults (aged between 15 and 64 years), namely the 28.9%, have taken at least one illicit substance once in a lifetime. For example, the estimate consumption, in course of life, of cocaine is about 9.6 million males and 4.3 million females, for amphetamines 5.9 million males and 2.7 million females and It is also estimated that the prevalence of opioid use ad high risk among adults (15-64 years) in 2019 represented 0.35% of the EU population, equivalent to 1 million high-risk opioid users. In 2019, there were 510,000 users on substitution treatment for addiction in the European Union from opiates, that represent 26% of requests for treatment of the drug addiction. On the other hand, opiates accounted for 76% of overdose deaths reported in the European Union in 2019. To these data is added the consumption of benzodiazepines and opioid analgesics (painkillers) out of prescription which, for example in the USA, is causing an annual number of overdoses at least 3 times higher than those for heroin and cocaine combined [3,4]. Various factors are involved in the development of addiction, relating both to the consuming subject and to the substance. Focusing on the latter, there are 3 main variables that come into play:

- the pharmacodynamic power, that is the ability of the substance to bind and activate certain receptors and to increase the mesolimbic dopaminergic transmission, ie neurons that project from the ventral tegmental area and the nucleus accumbens to the prefrontal cortex. Complete agonists are typically more additive than partial agonists while antagonists do not induce known addictive or tolerant phenomena. As for the receptor binding power, it is known that the greater the affinity and duration of it, the greater the probability of inducing addiction;
- half-life, i.e. the time the substance or its active metabolites remain in circulation, where the lower it is, the greater the chances of developing abstinence and the need for prolonged self-administration;
- the pharmaceutical form, that is the method of release of the active ingredient and of its absorption and metabolism [5].

It is precisely in relation to this last aspect that we want to deepen this article by evaluating whether different pharmaceutical forms of the same substance can induce changes such as to influence the methods of administration and the relative danger of abuse.

Materials and methods

This article was performed according to the PRISMA guidelines, thus providing a comprehensive framework which objectively assesses indications of quality of included studies. The characteristics of the studies eligible for the review included being related to the thematic of addiction, regarding mainly related to pharmacokinetics, dynamics and pharmaceutical form. We used studies published between 1980 and 2022 [6]. The studies were excluded if they did not relate to any of the specific subjects of addiction considered in the review (neurobiology, risk factors, consequences and relationship to free will/ self-determination). Studies were identified by searching papers according to their relevance via PubMed/ MEDLINE (http://www.ncbi. nlm.nih.gov/pubmed). After performing the initial literature search, the first 400 study titles and abstracts (seriated according to ''best match'') were screened for eligibility by the first author. Full texts of all potentially relevant studies were subsequently retrieved and further examined for eligibility: 38 studies were suitable for the inclusion in this review. Besides the mentioned studies, one textbook of psychiatry was also included in the review. The PRISMA flow diagram (Fig. 1) provides more detailed information regarding the selection process of the bibliography. Results In addition to the use of an Addiction textbook, the search in Pubmed/MEDLINE database resulted in 38 scientific articles meeting the inclusion criteria.

Discussion

The pharmaceutical form identifies the physical formulation in which each type of product, medicinal or otherwise, is presented. In fact, it contains the active principle responsible for the therapeutic or toxicological effect in addition to other substances present as excipients, which favor the maintenance of the pharmaceutical form itself and its stability / conservation and on the other hand intervene in the release of the active principle itself. It should be noted here that the excipients are not always chemically inert; for example, many liquid formulations of benzodiazepines contain 16% of ethanol together with flavoring, which often intervenes in the development of addiction (many patients, for example, for lormetazepam report direct intake from the bottle without diluting it precisely for the search for the taste of substance) [7]. The same goes for street illicit drugs which are always adulterated; in the case of opioids the purity never exceeds 40-70% while for cocaine and stimulants in general it is greater. Regarding the pharmaceutical forms in the development of addiction, some considerations must be made. In the case of purely recreational abusers, the effect of the substance is sought in a short time and therefore formulations that release the substance rapidly will be preferred [8]. This involves the choice, for example, of oral liquid formulations (drops) or solid forms (orosoluble tablets) as the release of the

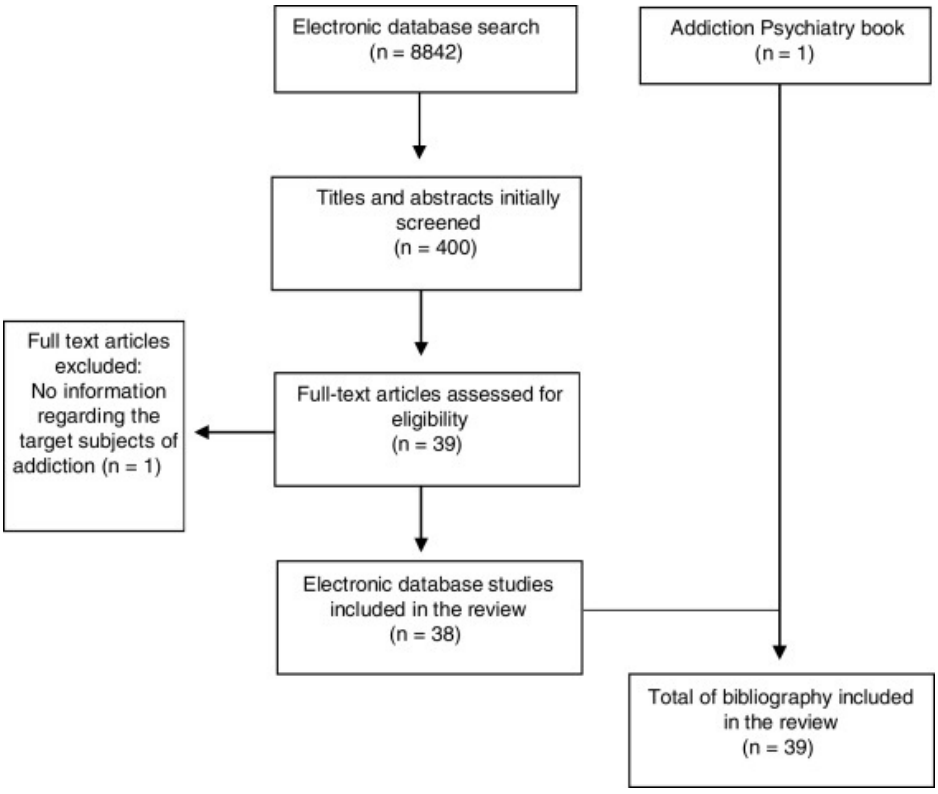

Figure 1.
PRISMA flow diagram for the article.

active ingredient from the pharmaceutical form occurs in a few minutes or even instantaneously [9]. The same applies in the case of patients with iatrogenic dependence on benzodiazepines and opioids: the data show that, in addition to preferring compounds with a short half-life such as lorazepam, alprazolam or morphine, oxycodone, etc., these subjects develop abusive behaviors especially in the case of immediate release formulations or make a misuse of prolonged release formulations by crushing them (either by chewing or pulverizing them before ingestion), thus eliminating their main pharmaceutical properties and making them immediately absorbable [10].

Biopharmaceutical of oral formulations

The pharmaceutical form used to deliver the active ingredient influences its bioavailability. The oral formulations can be divided into solid, semi-solid and liquid [10]. The solid forms, in turn, can be classified on the basis of the release of the active ingredient (immediate, prolonged, delayed or repeated) and the design (tablets, hard or soft capsules, pods, etc.). It should be borne in mind that, for an active ingredient to be absorbed enterally, it must always be in solution in gastric and enteric fluids. This implies that the greater the steps that it must carry out to "free itself" from the original shape, the greater the absorption time and therefore the delay in the onset of the effect. In the case of liquid solutions, the active principle is already immediately available for mucosal absorption and no release must take place; in the case of suspensions, on the other hand, the speed of dissolution is the major variable that influences the speed of absorption (the size of the fine or micronized particles accelerates this passage). In the case of tablets, the first step is the disintegration of the pharmaceutical powder particles into smaller aggregate particles, followed, after wetting in the digestive fluids, by their dissolution (Fig. 2) [11,12,13].

In the case of the coated forms, the presence of an external gastro-resistant polymeric film creates a physical barrier between the tablet and the aforementioned fluids, adding a further dissolution step and this allows to control the site or the speed of release. In the case of tablets, two clarifications must be made:

- the most rapidly absorbed forms are the sublingual (bypassing the first hepatic passage and the gastrointestinal transit, being immediately released into the circulation with a rapid effect) and orodispersible/orosoluble (dissolved in the mouth and then ingested: they follow the normal enteral path of a tablet but have the advantage of reaching the stomach already in solution and therefore are absorbed quickly) [14];
- the modified release formulations are coated with a specific film-forming layer which, if altered for example by trituration, causes the very rapid release of large

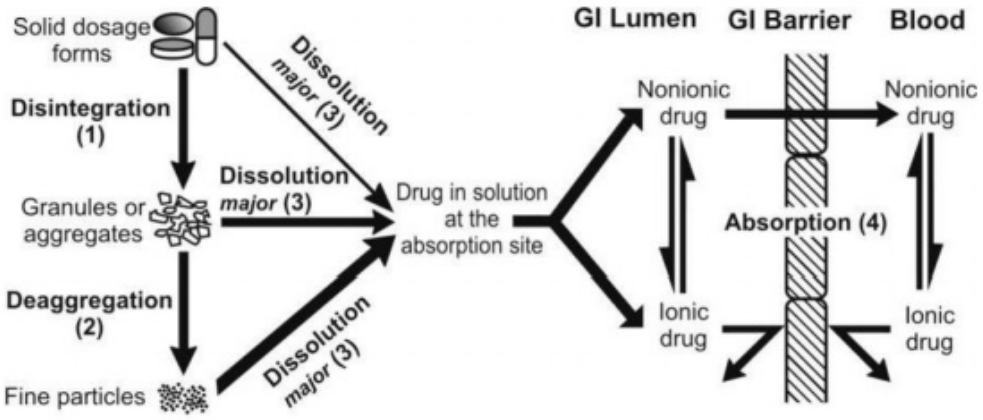

Figure 2.
Drug release from solid pharmaceutical forms.

doses of active principle which will be more rapidly absorbed [15].

Finally, a clarification must be made on syrups, given that methadone is in this form: they are liquid solutions containing high concentrations (over 45%) of sugars and polyalcohols (e.g. glycerol) which, in addition to masking the unpleasant taste of some active ingredients, they prevent crystallization and microbial contamination, favoring their conservation [16].

Some specific cases concerning illicit substances or drugs subject to misuse will now be considered.

- *Opioids drugs:* the phenomenon of the abuse of this substances, includes painkillers, in the USA is epidemic in the last years and the overdoses of these compounds have exceeded by at least 3 times those of heroin. The phenomena which we witness most are attributable to 2 types. One is the misuse/diversion of opioids used in the replacement therapy of subjects with previous heroin addiction, such as methadone or buprenorphine/suboxone tablets, which are sometimes taken in different ways from those prescribed [17,18]. It should be remembered that by misuse we mean the use of a drug in a different way from the prescription, modifying the modalities of assumption or the dosages while by diversion we mean the unauthorized way in which subjects obtain the drug [19]. In particular the major problems are firstly the intravenous misuse of methadone, with the high risk of blood hyperviscosity and possible ischemia or phlebitis, sometimes with local gangrene at the injection site and secondary hyperglycemia given the high sugar concentration, and also of buprenorphine after pulverized adverse reactions, with the risk of embolisms and acute intoxication reactions (the intravenous route determines a 100% availability of the substance as opposed to the enteric one). It must be said that in the literature there is a greater risk of misuse with buprenorphine than methadone, however also the suboxone formulation was found to be not free from misuse phenomena, even if in smaller proportions [20]. Surely buprenorphine alone is subject to injective use. generally in small doses at a time, using fragments of tablets to avoid saturating the receptors and maintain the gratifying effect by minimizing the unwelcome ones (in some countries, not in Italy, suboxone is also available in soluble leaflets to be adhered to the oral mucosa and difficult to detach precisely to prevent diversion and misuse after controlled recruitment, however the very thin thickness makes it easy to introduce them illegally, for example in prison). Six-monthly subcutaneous opioid implants are being studied to maintain abstinence [21]. The second problem is the use of painkillers outside of medical prescriptions for recreational purposes or in patients with chronic pain and the development of tolerance and addiction [22]. The commercial introduction of prolonged-release formulations of potent drugs such as oxycodone or hydromorphone has sometimes led to their administration after pulverization or by chewing, causing rapid highs and absorption. The same goes for the sublingual tablets and fentanyl lollipops, over 70 times more potent than morphine, which has made these compounds popular in the new psychoactive substances. It must be said that the risk of addiction is much greater for these formulations than, for example, transdermal patches due to the different kinetics of drug release, slower and more constant for the patches and faster and shorter for the sublingual forms or nasal sprays (Fig. 3) [23].
- *Benzodiazepine:* BDZ are marketed in injectable vials, tablets / capsules or oral drops and, with some exceptions, such as all active ingredients (about 30 in Italy) have more than one pharmaceutical form available. We will not go into the pharmacological details of BDZ here but remember that, aside from the ampoules which are used only in healthcare settings and rarely at home, the solid and liquid oral formulations

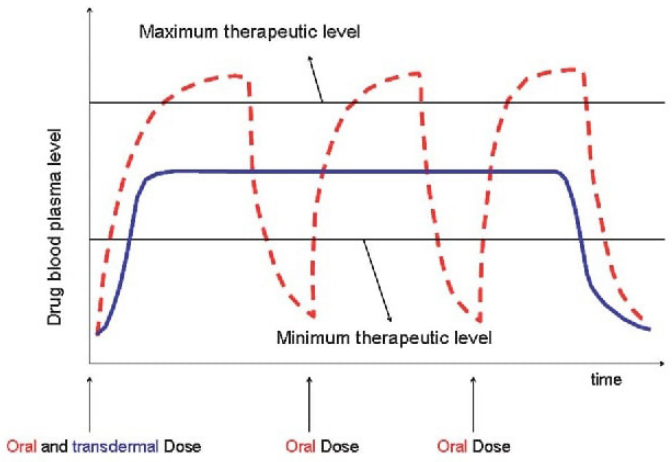

Figure 3.
Oral vs transdermal drugs release.

do not present the same risk of abuse. In particular, the tablets/capsules allow a more precise dosage and also sometimes the possibility of being divided and therefore the scaling of the dose [24]. Furthermore, there are modified release formulations that induce slow absorption and delayed plasma peak: these formulations have proved to be less additive probably as they induce less release of dopamine in the meso-limbic circuits and less "high effect" [24]. The drops, on the other hand, are more concentrated and often, being the BDZs not very soluble in water, they contain ethanol as a solubilizer up to 16% (itself responsible for any additivity, especially if they are taken undiluted but directly from the bottle) [25]. They also contain flavoring to increase the palatability. These factors put together, in addition to the greater speed of absorption since they are aqueous solutions, make it easier to abuse. Also the slowness of dripping and the presence of alcohol have been offered/suggested as possible causes for the increased risk of developing dependence to the oral formulation of lormetazepam rather than to other anxiolytic and hypnotic drugs. Costa et al. in a study have assessed the time of dripping of the most used benzodiazepines and z-drugs oral solution products under experimental conditions and the different employed excipients through a comparative analysis of the Summaries of Product Characteristics. A wide range of the median overall dispensing time was found across the eight products included in the analysis. The data suggest that the pace of dripping and the presence of alcohol can be considered themselves causes that triggered the drugs abuse. More precisely, the quantity of alcohol per bottle has been found negligible at therapeutic doses; however, when these are exceeded, they may have clinical implications for patients [26].

- *Other drugs:* even if less commonly than the previous ones, in recent years other psychotropic drugs have been reported, mostly by case reports, as a cause of mainly physical addiction and for which the pharmaceutical form has proved to be involved [27,28]. We report, for example, the case of quetiapine, a second generation antipsychotic dopaminergic antagonist D1 and 2 and serotonergic 5HT1A and 2, as well as alpha-adrenergic and histaminergic. In Italy it is available in fast and modified release presses [29,30]. The first evidence of quetiapine abuse appears in September 2004 in the American Journal of Psychiatry. In the letter to the editor, more than 30% of patients held in a Los Angeles County prison were used by mouth or by inhalation of the pulverized tablets. The effects sought were associated with the anxiolytic and sedative properties of the substance, i.e. as an aid to sleep or to calm the effects of other substances of abuse, rather than for antipsychotic properties [31,32,33]. The inmates simulating psychotic problems, had easy access to the prescription of the substance making it attractive even on the illegal market between inmates and ex-inmates once out of prison. A potential use of quetiapine for the treatment of opioid and cocaine addiction is currently being investigated in the clinical setting [34,35]. A 2005 study, published in the Journal of Clinical Psychiatry, reports positive results in the use of the drug for the treatment of opiate addiction, but some scholars are perplexed about the drug's possible addictive properties [36]. The trituration of the prolonged-release tablets and their rapid absorption favors the rapid onset of anxiolytic and calming effects but also that of withdrawal symptoms such as headache, nausea, vomiting, nervousness, tachycardia. The rapid response to drug rechallenge is typically typical [37].

Conclusions

In recent years, the attention in research on substance addictions has focused a lot on their pharmacological properties and on what factors could influence their dynamic and kinetic behavior once taken. In addition to the half-life, which however remains fundamental, the pharmaceutical formulation and the methods of recruitment are also the masters allowing to modify the metabolic behavior, the onset of psychic or physical effects and their intensity and above all the additivity [38,39]. With the exception of the injectable formulations, which remain the most problematic, and the transdermal ones, which are not very additive due to the slow absorption kinetics and the long constancy of effects, the oral formulations in drops or buccal formulations are the most additive together with the pulverization of the release ones prolonged, because they all determine the rapid release and absorption of high doses of the active ingredient and the onset of high. Conversely, those with prolonged release and/or long half-life and transdermal ones can be useful in the cessation of addiction by stabilizing the patient more from withdrawal symptoms for greater receptor occupation.

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Original article

Società Italiana di Psichiatria

Human homicidal destructiveness and humanity murder

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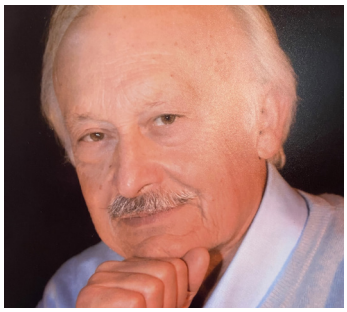

Giancarlo Nivoli

A human causing the death of other human may be with murder of one person, numerous people or an entire popolations at war, it is clearly stated in the history of mankind [1-10]. It consist of murders, according to forensic psychiatry, consiusly, voluntarily and avoidably performed. The presence of this homicidal human destructiveness, from the beginning of our civilization since the present age has allowed classical pychoanalytic psychiatry to assert, no without criticism, that the "history of human population'' is, in fact, the ''history of homicide between people'' and that the omnipresent rule among populations "don't kill'' is the proof that "we all descend from generations of murderers'' [11,12]. Humans history teaches especially that in wars between people we have the highest espression of destruction of tangible property and human lives. Human homicidal destructiveness it is present in every war and not one nation of world importance is innocent. The study of war causes (polemology) and peace (irenology), highlights the motivational complexity that underlies the murders between peoples. It also points out that the motives of war are not only factors of political interest, economy, geopolitics, acquisition of foodstuff, energy related, etc. But also factors related to the psychology of aggressive human behavior and the criminal psychology of crowds [13].
The mankind history teaches that is possible to state that the human homicidal destructiveness exist and also there are humans (king, dictator, despot, tyrant, conqueror, leaders of criminal organizations or religious sect, etc.) that are more likely to apply it, regardless of the reason with wich self-legitimize the deaths provoked to other humans. According to the principle of homicidology we can call these humans "Humanity Murder", in order to distinguish them from author of multiple homicides like mass murder, serial killer, lust murder, etc. Not all the king, dictator, etc. is an humanity murder [14]. According to treatment of multidisciplinary forensic psychiatry, of these humans, humanity murder, we will illustrate the characteristics for their diagnosis.

Fifteen psychological and behavioral characteristics of humanity murder

The history of humans, past and presence, highlights the behavioral and psychic structure, the more evident one is under the eyes of every population, of the humanity murder. We are talking about the most dangerous murder for the human species due to their ability to take command position, manipulate the mass and cause a voluntary, conscious and avoidable human homicidal destructivness.

1. lack of empathy for the suffering of others and the humanitarian tragedy;
2. self-legitimation in causing the death of others humans;
3. attribution of blame for own crimes to other people;
4. sistematic use of lies and deception in comunication;

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5. skills for dissocial manipulation of crown;
6. abolition of every manifestation of thougt and press liberty;
7. phisical distruction of dissidents;
8. acquisition of complicity with even illegitimate privileges;
9. tendency to intensify and widen the war;
10. creation of a threat and terror climate for own personal affermation;
11. reactive feelings of personal onnipotence;
12. personal searching power through threat of distruction of properthy and life of dissidents in and out of own people;
13. desire and psychological necessity to keep power for ever and at any cost;
14. feeling of impunity for committed crimes;
15. obsessive and compulsive rigid messianic identification to a grandiose narcissistic ideal of himself which he can hardly give up, also if it demand sacrifies life of so many life of other humans, own properties and life.

It consist in 15 variables whose importance, qualitative and quantitative, for diagnostic purpose follows normal rules and critical issues of diagnostic statistic classification of homicidology manuals [1,8,10,12,15-30].

Essential psychic features of humanity murder: the culture of threat, terror and death as a means of one's social affirmation and personal power

The past mankind history and the present teach that humanity murder always research a "super dose of murders completely avoidable", not respecting the political modalities of real social problem resolution, the maintaining of personal power and not acting with respect of internationals laws of humans rights and of war. This "culture of threat, terror and death", despite the most imaginative and unrealistic self-legitimations, is managed by humanity murder whith the purpose, according to dynamic forensic psychiatry, of "personal social affermation" and the management of a grandiose power on himself. The whole thing, always according the dynamic forensic psychiatry, to create an important identity "to change a fragile and unsatisfactory identity" and "take revenge of all the frustration and real or immaginary humiliation suffered" [10].

According to categorical clinical psychiatry or the dimensional psychiatry which integrates with the previous dynamic forensic psychiatry, the humanity murder present on a clinical level the "spectrum of dissociality": a big container of all the humans that not respect laws, they feel not empathy for own similar, they value violence and deceit in personal relationship, etc. In concrete diagnostic term, it involves in various psychiatric diagnosis like psychopathy, sociopathy, narcissistic personality disorder, paranoid personality disorder, sadic personality disorder, dark personality, machiavellic personality, etc. [26,27]. Those dissocial humans, if they're not smart, able simulator and dissimulator, without the ability of climb the hierarchical position of power, etc. they lives in the cells in all prisons in all the world. If those dissocial humans are smart, they know how to climb with abilities the hierarchical position of power, they are able simulator and dissimulator, etc. they can become humanity murders and cause extensive damages for other humans with their homicidal destructiveness.

According to the expert multidisciplinary forensic psychiatry these individuals are, apart from some inevitable exception, capable of understanding and wanting in front of the law, and so punishable for the commited crimes and required to refund the caused damage. We cannot make confusion between mentally ill people and criminal people. We cannot mistake criminal motivations about a beahaviour for mental illness diagnosis [1,7,22,31]. Mental illness that could remove, but not always, a personal responsibility.

The forensic psychiatric prevention of human homicidial destructiveness

At this moment of the human evolution it's quite difficult avoiding the human homicidal destructiveness and the genesis and growth of humanity murder in specific and predisposed populations. However something can and must be done about prevention. Under forensic psychiatric aspect it could be evaluated, simplifying the issue, two different types of prevention: a prevention of an already started worsening of human homicidal destructiveness and a general prevention to avoid a human homicidal destructiveness in the future. For what concern the first form of prevention we can consider the following remarks.

1. Avoid the human homicidal destructiveness "uncontrollability" that occurs with letal weapon intensity increasing and the improvement of main protagonists involved in war scenarios. All the numerous "psychological traps" put in place by aggressors, by the attacked ones and by apparently neutral protagonists that tend to increase human homicidal destructiveness, must be known and avoided.
2. Keeping a steady and functional "dialogue of respect and mediation", like a psychiatric psychotherapeutic interview, between the conflicting parties. Human homicidal destructiveness and humanity murder are motivated non only for deep psychological conflicts tied to human aggressiveness but also for economical, social, etnical, geopolitical conflicts which cannot be overlooked by the mediation art.
3. "Condemnation at international levels of crimes against humanity and war crimes". It's not about solving murder and war crimes issues between human beings. It deals with, in immediacy, condemning and charging for damages all the people that do not respect the shared laws that stand for human beahaviour.

4. "Ethical and juridical responsability of the humanity murder and all its accomplices" that cause and keep human homicidal destructiveness. Accomplicity means all the numerous politicians, state administrators, representatives of armed forces, industrial leaders, public information exponents, etc. included their friends and families, who with thier own agreement and actions support human homicidal destructiveness.
5. "Application of new ethical, juridical, defensive victimologists and military behavioral precepts to defend against human homicidal destructiveness, humanity murder and accomplices." It's about progressivenss of punitive penalties; creation of news preventive lawful defense principles; applications of Mutual Assured Destruction to single people; implementation of asymmetric, unconventional and irregular war, etc.
6. Identification of "deviant pacifism" which supports human homicidal destructiveness, humanity murder and accomplices. It's not about "real pacifism" that has to be enhanced and desired as social maturity of a single one and people. it's about victimological pacifism from fear, from illegitimate personal interests, etc. that, tangibly and realistically, support humanity murder and accomplices worsening.

In form of general prevention, we can report the following remarks:

- the current evolution of the human species, as history teaches, highlights the danger in the past of the tendency to "deification" and in the present to the "cult of the personality" of leaders who can concretely perceive themselves above the shared laws that regulate social life. No too much power in one person;
- "need for political, legal, psychiatric controls, etc." provided for by law and with freedom of the press, over people who can manage a lot of power over other humans. These are measures not different from the institutional control of a citizen's ability to drive a car or to obtain and maintain a license for a personal weapon;
- "education of the population in the culture of legality". It is not just a culture of respect for rights and duties according to the law. It is also a culture, like ownership in psychotherapeutics setting, of "personal responsibility": it will no longer be possible to accept the justification "I committed this crime because I was ordered". Implementation of personal responsibility that involves many ethical, social and legal problems;
- ethical and legal responsability of the authors of the "information war". In addition to the personal responsibility of those who make the "war with bombs", it is also a question of making responsible those who, making "war with informations", in bad faith, against laws and illegitimate interests, collaborate in the information war that facilitates human homicidal destructiveness;
- "presence of supranationality social-juridical institutions that can provide protection for material assets and the social, mental and physical health of citizens." These are supranationality institutions that can give, according to phenomenological psychiatry, "a value and a meaning", among the many possible, shared by nations, on the rights and duties among human beings. It is not a question of creating these institutions that are already present in today's world but of improving their functionality, their powers of preventive intervention, their ability to prevent events and their concrete possibilities of executing sentences of punishment and compensation of the damage;
- the foregoing remarks is a sort of limited psycho-social psychiatric forensic rehabilitation project of human homicidal destructiveness. The foregoing remarks must be completed in order to have value on improving the quality of life of humans from numerous other disciplines of human knowledge such as political science, historical science, sociology, crowd psychology, geopolitics, international law , etc. The foregoing remarks can be deepened, especially in terms of bibliography, by the writings of the same author on the same topics published in 2003.

Conclusions

The type of murder described, "humanity murder", can be more scientifically investigated and it can not be overlooked in the explanation and prevention of human homicidal destructiveness.

The "depressive and masochist attitude" ("the atrocities of war and the humanity murder there are been in the past and always will be in future") may be modified in an "depressive and restorative attitude" ("it is true that the atrocity of war there have always been, but we can do something to prevent and restrict them").

All foregoing remarks must be interpreted in "the frame of values and meaning" of protection of "social health" of human species. Mankind: a living biological species so "recent" in the history of earth, "temporary" in the history of the evolution of the physical universe, so currently "agressive, destructive and homicidal intraspecific".

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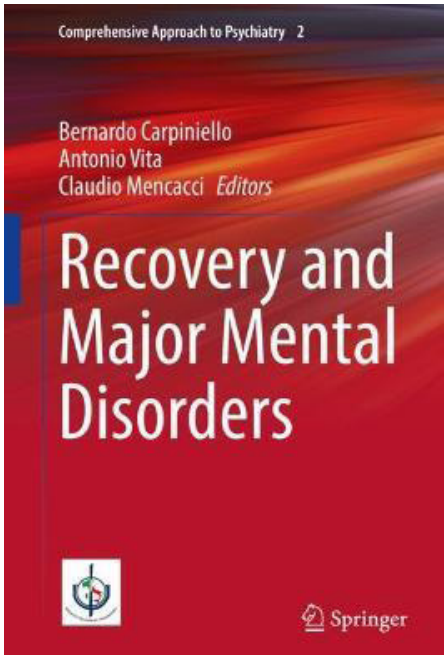
Società Italiana di Psichiatria

Book Review

Recovery and Major Mental Disorders

Bernardo Carpiniello, Claudio Mencacci, Antonio Vita (editors)

Springer, 2022



In the field of psychiatry, the term Recovery can have two main meanings. The first refers to a multidimensional clinical construct used as a complete and reliable measure of the outcome, especially in case of integrated interventions; the other one concerns the personal process of "living together" with a mental disorder, described through the subjective experiences of those who live this journey with and through their disorder. The first approach was developed in clinical contexts, the second within the movement of users and their families. Both approaches have significantly contributed to a paradigm shifting in both care and clinical research, as evidenced by the growing number of citations regarding recovery related papers over the past twenty years, more than 23,000 only referring to Pubmed. Despite the evident international agreement about the relevance of the issue of recovery, not all that glitters is gold. Although many mental health services declare themselves to be recovery-oriented, it is uncommon that in ordinary practice a real and concrete orientation of interventions towards this goal is ensured. Moreover, although the term recovery is now an integral part of the psychiatric lexicon and has become commonly used, it should be recognized that an in-depth knowledge is still lacking regarding the complexity of the problems inherently related to recovery, the disputes and the knowledge gaps still existing and the persistent conceptual and methodological difficulties. Moreover, the theme of recovery, historically linked to the field of schizophrenia and related disorders, in recent years has progressively extended to other clinical areas, in particular to mood disorders, for which recovery has taken on meanings and methodologies of assessment which are somewhat different with respect to the field of non-affective psychosis. The volume here presented, "Recovery and Major Mental Disorders", aims at offering to the readeres a compherensive approach to the issue or recovery both as regard to schizophrenia and mood disorder. This Volume is the second one in the series "Comprehensive Approach to Psychiatry", published by Springer, which was launched two years ago under the aegis of the Italian Society of Psychiatry with the volume "Violence and Mental Disorders". This Volume, edited by Bernardo Carpiniello, Claudio Mencacci and Antonio Vita, contains the contributions of some of the leading Italian and foreign researchers and clinicians in this field, aiming with its thirteen chapters at being the most up-to-date and in-depth book on recovery in the current scientific arena.

Bernardo Carpiniello

Errata Corrige

Errata

Evidence-based Psychiatric Care 2022;8:836-40 doi: 10.36180/2421-4469-2022-3

Esketamine in treatment resistant depression: a study protocol for a retrospective, real-life, multicentric study

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Corrige

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Esketamine in treatment resistant depression: a study protocol for a retrospective, real-life, multicentric study

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