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EVIDENCE-BASED PSYCHIATRIC CARE

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TOLERABILITY OF LAIS: MANAGEMENT ISSUES IN CLINICAL PRACTICE

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Summary
Antipsychotics are the mainstay of treatment in schizophrenia and are used to treat acute psychotic symptoms as well as protect against relapse. Nonadherence to treatment is common, and reinforces cycles of recidivism. Long-acting injectable antipsychotic therapy may facilitate continuity of treatment and support better outcomes, particularly in patients with chronic illnesses, whose management is frequently complicated by factors such as comorbid substance abuse. Therefore, these formulations can both decrease the chance of a patient's illness relapsing and improve their recovery. Additionally, some patients prefer to choose this type of formulation over having to take tablets on a daily basis. The choice of LAI must be individualized for each patient, taking into account both the efficacy and the specific tolerability of the patient, but also considering the patient's preference, cost and treatment adherence and potential risk of incorrect drug assumption.

Key words: long-acting antipsychotics, safety, tolerability, side effects

Introduction

The chronic development of schizophrenia and its ability to generate high disability [1] needs an adequate pharmacological treatment during the acute phases to be continued in the medium and long term. Unfortunately, adherence to psycho-pharmacological treatments has always been one of the main psychiatric barriers in managing complex disorders such as schizophrenia. Regarding to oral therapy with antipsychotics, the literature reported discontinuation rates of 74% at 18 months of treatment [2] and 42% at one year, regardless of Second generation Antipsychotics (SGAs) or First Generation Antipsychotics (FGAs) treatment [3]. The consequences of this condition are devastating both in clinical, relational and functional terms. Although long acting formulations were introduced at the end of the 1960s, they were considered therapeutic options to be used only when all the previous ones had failed. Despite the obvious benefits on side effects and the role of preventing the relapse, long acting antipsychotics continue to be an underutilized option with employment rates ranging between 10% and 25% [4 5]. One of the reasons for their poor use may be our concern for the possible onset and the management of side effects during long acting therapy. These effects must be considered and adequately monitored and managed, but they can not be an obstacle to their use.

Rationale

Tolerability and effectiveness of antipsychotics are important to increase treatment compliance in people with schizophrenia. Symptoms of schizophrenia can be treated effectively with antipsychotic medication;

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however, poor adherence to prescribed treatment is one of the biggest challenges of managing the symptoms of schizophrenia and delaying time to relapse [6]. Discontinuation of antipsychotic treatment for schizophrenia can interrupt improvement and exacerbate the illness. In general, oral FGAs are associated with a different side effects profile than SGAs with a higher risk of movement disorders, for example, extrapyramidal symptoms (EPS) and tardive dyskinesia, although SGAs have been more linked to weight gain and metabolic risk.

Long-acting injectable antipsychotics (LAIAs) were introduced to improve treatment adherence and tolerability of oral formulations. Long-acting injectable antipsychotics deliver therapeutic concentrations over several weeks, eliminating the need for daily dosing and providing clinicians with certain knowledge of adherence or nonadherence. These agents increase the likelihood of continuous and effective treatment and may reduce patients' risk for relapse. This, in turn, could decrease the likelihood of institutionalization in hospitals and incarceration [7]. The difference of pharmacokinetics of LAIs compared with oral antipsychotics, such as the long elimination half-life, can delay both the onset and the remission of adverse effects.

Objectives

The aims of the presented research are to generate estimates of relative tolerability, and safety for second-generation LAI antipsychotic treatments using available evidence althought only a few direct comparisons between one LAI and another have been conducted.

After risperidone was introduced as the first long-acting injectable second-generation antipsychotic, during the last five years olanzapine pamoate, once-monthly paliperidone palmitate and once-monthly aripiprazole has also been marketed [8].

Method

A review of all english-language published literature during the last five years (from 2012 to the present) was conducted with the electronic searches by using PubMed for current data regarding the topic of LAIs and the role of tolerability. Keywords used for the search were "long-acting injectable antipsychotics" and "second-generation antipsychotics" in association with one of the following: "Tolerability,"and "side effects." References to key articles were further explored for relevancy to this proposal. In addition to long-acting injection (depot) antipsychotics and second-generation (atypical) antipsychotics, a separate search was performed for each available drug: aripiprazole LAI, olanzapine pamoate, paliperidone palmitate, and risperidone LAI. Articles were excluded if they were single case reports, case series studies, small naturalistic studies and studies providing no safety data. The safety and tolerability outcomes included incidence of clinically relevant weight gain and incidence of EPS during the treatment or clinically relevant adverse events (AEs) in term of treatment discontinuation.

Peculiarities of long acting formulations

The drug release mechanism in long acting formulations allows a reduction in first-pass absorption and metabolism variability (Table I). Advantage results in greater reliability in achieving more stable plasma concentrations over time [9]. Compared to oral formulations, the long acting ones create a better correlation between the administered dose and the plasma levels of the drug. Once steady-state is reached, the plasma level of the molecule remains relatively stable, avoiding fluctuations related to daily administration [10]. Table I shows the differences existing between the different molecules (risperidone, olanzapine, paliperidone, aripiprazole) in relation to their mechanism of drug release. The release mechanism influences the fluctuations of the drug once the steady-state is reached. In the case of olanzapine pamoate, the 4-week formulation compared to the 2-week formulation or the same oral formulation, determinate a significant variation [11]. While, in the case of paliperidone palmitate, compared to the oral formulation, which already had a controlled release, the variation is minimal. Furthermore, it should be considered the pharmacodynamic properties of the individual molecules, and in particular their affinity to the dopaminergic, serotoninergic, istaminergic and muscarinic receptors for the specificity of the side effects (Table II). Some authors report that the benefits described may conflict with the concern of clinicians for the use of a high dose at the time of administration and therefore the inability to obtain a rapid reduction in the dose of the drug as well as its interruption at the time of occurrence of a side effect [10].

Result

LAI Risperidone Tolerability

Risperidone long-acting injection (RLAI) was the first second-generation antipsychotic available as a

Table I. Pharmacokinetic Characteristics and Release Mechanism of Long-acting Second Generation Antipsychotics.

	Olanzapina pamoato	Risperidone microspheres	Paliperidone palmitate	Aripiprazole
Formulation	Suspension of microcrystals in water suspension	Microspheres in water suspension	Water suspension using crystals of the molecule	Powder in water suspension
Release mechanism	Salts: dissociation in olanzapine and pamoic acid	Microspheres erosion and diffusion	Prodrugs: hydrolysis by esterase	Powder of particles with low solubility
Frequency of administration	Every 2-4 weeks	Every 2 weeks	Every 4 weeks	Every 4 weeks
Conservation	Ambient temperature (15-30 ° C)	2-8 °C	Ambient temperature (15-30°C)	After reconstitution but can be stored at temperatures below 25 ° C for up to 2 hours in the syringe
Tmax (days)	4	21	13	5-7
Elimination half life (days)	30	28-42	25-49 (range dose 25-150 mg)	46,5 for 400 mg 29,9 for 300 mg

long-acting injection. It was developed in 2002. It has been shown good tolerability and almost no interruption due to adverse effects or to relevant biological parameters alterations. Also, weight gain was not significant. Fernández-Miranda et al (2015) [12] indicate Clinical Global Impression Severity ($p < 0.01$) and Camberwell Assessment of Need ($p < 0.01$) decreased and also Disability Assessment Schedule in the 4 areas ($p < 0.01$). Regarding Medication Adherence Rating Scale the score increased from 3.6 to 8.9 ($p < 0.001$). Morover, it has been seen significantly few hospital admissions than during the previous 36 months (1.9 *vs* 0.31, $p < 0.001$).

Other authors demonstrated that In patients with recently diagnosed schizophrenia, the tolerability and efficacy of Paliperidone Palmitate (PLAI) and RLAI is generally similar over 13 weeks. The overall adverse events rates at week 13 for PLAI and RLAI were 54.7 and 50.3%, respectively, for any AE; 11.2 and 8.1% for extrapyramidal symptom-related adverse events (AEs); and 2.5 and 2.3% for prolactin-related AEs. No significant differences in the mean weight change,

Table II. Pharmacodynamic characteristics of second-generation antipsychotics available in long acting formulations.

	Olanzapine	Risperidone	Paliperidone	Aripiprazole
D2	20	3.77	2.8	0.66
5HT1A	610	190	480	5.5
5HT2A	1.5	0.15	1.2	8.7
5HT2C	4.1	32	48	22
α1	44	2.7	10	26
α2	280	8	80	74
H1	0.08	5.2	3.4	30
M1	2.5	> 10,000	> 10,000	6,780
M2	622	> 10,000	> 10,000	3,510
M3	126	> 10,000	> 10,000	4,680
M4	350	> 10,000	> 10,000	1,520
Main side effects	Sedation, weight gain, dyslipidemia	EPS, Akathisia, Hyperprolactinemia	EPS, Akathisia	Akatisia

Table III. Procedures for subjects with AP LAI [26].

General Clinical evaluation	Personal and family medical history (diabetes, dyslipidaemia, cardiovascular disease)
	Healthy lifestyle (eating habits, physical activity, substance use, smoking, alcol)
	Weight, Body Mass Index calculation, waist circumference
	Blood pressure, Cardiac frequency, Body temperature
1st line clinical exams	Complete blood count, blood electrolyte (K, Na, Ca, Mg),urea, creatinine and fasting glucose
	Liver function tests
	Lipid profile
	Beta hCG
	Electrocardiogram and QTc evaluation
2nd line exams (depending on the clinical state of patient)	Thyroid function test
	Prolactinaemia
	Electroencephalogram

most metabolic parameters, or mean efficacy measures were observed at end point [13].

LAI Olanzapine Tolerability

Postinjection delirium/sedation syndrome (PDSS) is a potentially serious adverse event that has been shown to be associated with one currently available LAI antipsychotic, olanzapine pamoate [14]. In a routine clinical practice study over a 5 year period a total of 388 post injection delirium/sedation syndrome were indetified with 91% within 1 hour of injection and 52% occurred within 15 minutes [15]. Other symptoms of PDSS include extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypotension or possible convulsion. In most cases (80%) initial symptoms appeared within one hour of injection with complete recovery within 24-72h after injection. Due to the possible emergence of this framework in the olanzapine pamoate technique, it is necessary to monitor for 3 hours after injection.

In recent years, this aspect has also been investigated for long acting risperidone and paliperidone formulations.

In the course of studies on risperidone (RP), 15 trials with 3,164 subjects (approximately 115,000 injections) and post marketing studies, no PDSS cases were found. With paliperidone palmitate, only one episode of PDSS was highlighted in 10 trials [7]. Although there are reported cases of sedation/drowsiness with the use of both molecules, the incidence of these events was not different from placebo. In fact, some authors point out that PDSS syndrome, described for olanzapine, can not be generalized to all long acting second-generation antipsychotics [7].

LAI Paliperidone Tolerability

Paliperidone (9-hydroxyrisperidone) is the active metabolite of risperidone. The long-acting Paliperidone (PLAI) has been developed as a suspension of paliperidone palmitate nanocrystals in an aqueous formulation, administered monthly by intramuscular injection.

Has been shown that PLAI is effective in controlling the acute symptoms of schizophrenia as well as delaying time to relapse. PLAI and RLAI have similar safety and tolerability profile. Several studies have demonstrated that schizophrenia patients treated with PP show higher rates of improvement of psychotic symptoms compared to placebo and similar efficacy and tolerability outcomes when comparing PP to RLAI or oral paliperidone extended release [16]. Thus, PLAI may represent the rational development of RLAI with greater ease of use [17].

The Paliperidone Palmitate efficacy, tolerability, and patient acceptability has been demonstrated in relevant number of short and long term studies, both RCTs and open label studies a also in patients switched to once- monthly long-acting paliperidone palmitate (PLAI) following previously unsuccessful treatment with oral or other depot APs.

As mentioned above, it has been shown that the tolerability (including rates of EPMS and prolactin-related TEAEs) and efficacy of PLAI and RLAT were generally similar and the higher incidences of weight gain and depression were reported in recently diagnosed compared with more chronic patients [13]. The greater incidence of weight gain in recently diagnosed patients is in line with another study of early schizophrenia in which most weight gain occurred within the first 3 to

6 months of treatment as well as data showing that patients with a higher baseline BMI gain less weight than those with a lower BMI [18]. The data suggest that PLAI is also generally well tolerated in a patient population more representative of routine clinical practice with higher rates of comorbidities, comedications, and substance abuse. However, among the most frequently occurring treatment-emergent adverse events was somnolence/sedation (5-7% paliperidone palmitate group *vs* 3% placebo). Hargarter et al. (2016) [19] demonstrate that recently diagnosed patients treated with PLAI had a significantly higher treatment response and better functioning, as assessed by the Personal and Social Performance scale (PSP), compared with more chronic patients. These data support current discussions that earlier continuous and effective AP treatment may be associated with better outcomes in patients with schizophrenia.

LAI Aripiprazole Tolerability

LAI Aripiprazole appears cost-effective *versus* other SGA-LAIs, with improved health-related quality of life and functioning in a head-to-head study with paliperidone LAI. A 6 month (pre and post), mirror-image switch study demonstrated a reduction in hospitalization and associated costs compared with previous antipsychotic treatment [20]. Safety and tolerability are comparable to oral aripiprazole with no new safety signals [17]. The overall tolerability profiles of both products are consistent with what is known about oral aripiprazole. Due to its specific pharmacological and tolerability profile, Aripiprazole long acting once-monthly (AOM) represents a suitable alternative for patients with schizophrenia requiring a switch to a new LAI treatment because of lack of efficacy or persistent side effects from other LAI [21].

The tolerability profile of a therapeutic agent is important in guiding long-term treatment decisions. AOM 400 was generally safe and well tolerated by patients with BP-I during long-term treatment with few discontinuations because of treatment-emergent AE (TEAEs).

The overall discontinuation rate during the 26-week randomized withdrawal phase in a study evaluating oral aripiprazole for to the 51.9% of patients on AOM 400 who discontinued during the longer 52-week randomized withdrawal phase of the present study. The majority of patients (> 80% at each injection visit) received the recommended dose of 400 mg. No new safety signals were noted, and observed TEAEs were mostly mild to moderate. Mean weight gain was low in the randomized phase and was similar between treatment groups. There were no clinically meaningful changes in extrapyramidal symptom scales, metabolic parameters, or vital signs. Prolactin elevation and the associated sexual dysfunction are troublesome consequences of antipsychotic treatment. Among the atypical antipsychotics, aripiprazole is known to be prolactin-sparing, whereas others, including risperidone, study didreveal any clinically meaningful alterations in prolactin levels with AOM 400 *versus* placebo, and there were few TEAEs related to prolactin or sexual dysfunction [22].

LAI Paliperidone 3 Month Tolerability

Compared with placebo, PP3M showed a longer time to relapse and good safety and tolerability profiles. In a recent randomized clinical trial the most frequently reported TEAEs (≥2%) in the group receiving 3-month paliperidone palmitate during the maintenance phase were anxiety (6%), insomnia (5%), weight increased (4%), and head- ache (3%) [23]. In general the 3-month formulation was generally tolerable and has a safety profile consistent with other marketed paliperidone formulations [24]. In view of its efficacy, tolerability, and safety, together with the longer timespan between injections, PP-3M may contribute towards addressing the issue of poor adherence, even in early psychosis [25].

Procedures for monitoring

The monitoring procedures for LAI antipsychotics are the same as for oral antipsychotics. However in a specific survey on LAI, based on a literature review, performer by 42 national experts in France some procedures are recommended in particolar in subjects treating with LAI [26]. These procedures are generally indicated for all patients during antipsychotic treatment but it are more important for those receving LAI (Table III). The frequency will depend on the risk factors found in the patient and on the clinical signs or medical condition that appear during the treatment.

Discussion

Although first-generation depot antipsychotics that use oil-based formulations are associated with pain on injection, aqueous-based formulations of LAI antipsychotics generally have good injection site tolerability.

The availability of both deltoid and gluteal formulations of LAI medication could therefore facilitate patient acceptance and long-term adherence to injectable antipsychotic medication. No or mild administra-

tion site pain, minimal risk of embarrassment/damage to the therapeutic relationship and some sedation but no other side effects were ideal features of LAI antipsychotics were identified. Furthermore, injection into the deltoid muscle requires minimal removal of clothing as it seems that patients prefer.

A survey of physicians and nurses from around Europe also revealed that the deltoid site may improve acceptance of LAI antipsychotics and be preferred by their patients. In fact seems that the deltoid administration may reduce social embarrassment associated with LAI antipsychotics and it has been considered as more respectful to the patient [27].

Predictably, the reviewed information revealed that SGA-LAIs have safety profiles consistent with their oral parent formulations. However, they seem to also show unforeseen and worrisome safety signals. Indeed, the routine use of olanzapine-LAI in clinical practice could be limited not only by the well-known risk of postinjection syndrome, whose clinical management remains a matter of concern, but also by the risk of worsening of psychosis. The reviewed information seems to suggest that worsening of psychotic symptoms and depression could also be associated with both risperidone-LAI and paliperidone palmitate. The leading cause of death among patients enrolled in risperidone-LAI studies was suicide [28].

Patients with schizophrenia are known to have a shorter life expectancy than the general population [29]; likely linked to the increased incidence of cardiovascular risk factors as well as metabolic comorbidities reported. Anyway, an early initiation of continuous treatment may benefit patients, as a lack of AP treatment has been associated with greater all-cause mortality.

Conclusion

As second-generation antipsychotic long-acting injections (SGA-LAIs) are rapidly replacing depot first-generation antipsychotics as first-line agents in treating schizophrenia spectrum disorders, a systematic review of their adverse effects is timely.

Second-generation antipsychotic drugs in their long acting formulations are an obvious benefit to the clinician in managing a complex disabling disorder such as schizophrenia. Although has been reported, the adverse reactions from the injection of such molecules, it can not and should not be an impediment to their use since there are benefits in terms of preventing relapses and therefore better quality of life for patients. In fact, the aim of treating schizophrenia can not only be to control symptoms in acute phases, but it must necessarily be a pattern of maintaining response over time.

Conflict of interest

Guido Di Sciascio was a consultant and/or speaker in symposia sponsored by Arcapharma, Angelini, Janssen-Cilag, Otsuka, Polifarma. Claudia Palumbo and Salvatore Calò: none.

Take home messages for psychiatric care

- Nonadherence to antipsychotic medications is an enormous challenge for clinicians and patients in the treatment of schizophrenia
- The formulation of LAIs as a method of delivering antipsychotics can be used to improve adherence, to decrease the chance of a patient's illness relapsing, and improve their recovery
- The choice of LAI should be individualised to each patient, taking into account both efficacy and tolerability specific to the patient, practicalities, patient preference and cost
- It has been shown good tolerability and almost no interruption due to adverse effects of LAIs

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MYTHS SURROUNDING THE LATENCY OF ACTION OF ANTIDEPRESSANT THERAPY

Summary

Objectives: Major Depression after anxiety disorder, is the most common mental disorder in the world. Studies conducted on quality of life have shown that depression causes the greatest disability and most lost days of work compared to other physical or mental disorders.

Materials and methods: To date, it has not been possible to identify biomarkers that are capable of predicting in advance a response to antidepressant drugs. If it was possible to develop criteria to facilitate a more rapid identification of an effective drug treatment, there would be obvious advantages: it would shorten the length of patient suffering and would reduce lost treatment time spent on ineffective drug treatments. Several studies have analyzed the predictive value of the initial response to antidepressant drugs and it has been found that an improvement of the Hamilton Scale of 20%, 25% or 30% after 2 weeks is a positive predictor of outcome after 6 weeks.

Results: Therapeutic Drug Monitoring is the measurement of a specific drug serum concentration to ensure that appropriate drugs levels are maintened. For every drug it is possible to delineate a specific "Therapeutic Index," a ratio between the toxic and therapeutic doses of medications.

Conclusions: Prediction of Antidepressant Response can be improved by a combination of early response assessment and plasma drug monitoring.

Key words: Prediction of antidepressant response; onset of antidepressant response, Therapeutic Drug Monitoring (TDM)

Introduction

Depression after anxiety disorder, is the most common mental disorder in the world. The incidence of depression in women is double that in men. There are case reports describing depression in children as young as 3 years of age; there are prevalence studies on depression that include children from 7 years of age [1]. Depression is currently ranked as the fourth leading cause of disease burden worldwide and it is estimated that by 2020, it will be second only to cardiovascular disease as the leading cause of disability [2].

According to the World Health Report 2001, published by the World Health Organization (WHO), neuropsychiatric disorders are among the diseases with the most serious psychosocial implications (DALY = disability adjusted life years). Of these, depression is the disease that affects the greatest number of years of life (WHO 2001) [3]. Studies conducted on quality of life have shown that depression causes the greatest disability and most lost days of work compared to other physical or mental disorders [4]. It is estimated that between 40 and 70 percent of people who commit suicide suffer from depression and that the risk of suicide is 20 times higher in depressed people compared to the general population [5-7].

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In depression, quality of life impairment correlates with symptom severity [8]. 50-75% of patients suffering from depression obtain adequate remission of symptoms [9 10]. However, some patients have persistent residual symptoms, of which anxiety is the most frequent symptom [11 12]. 20-30% of depressed patients show an immediate response to drug therapy [13], while only 10-20% obtain permanent remission [14]. The high incidence of incomplete response carries an increase risk of relapse [15]. Recent research shows that only a third of patients respond to the first antidepressant drug prescribed (33%), another third to the second (24%), 7% to the third and only 4% to the fourth (Gaynes et al. 2008) [16]. The probability of obtaining remission after only 6 months is reduced already by 50%. After nine months it further reduces to 15%, then it reduces to approximately 1% for each month thereafter [17 18]. The duration of the depressive episode seems to consistently correlate with clinical response and efficacy of antidepressant treatment; for this reason the issue of latency of antidepressant action is of fundamental importance.

Antidepressants are commonly prescribed using a "trial and error" approach. To date, it has not been possible to identify biomarkers that are capable of predicting in advance a response to antidepressant drugs [19]. According to widespread opinion, antidepressant treatment must be taken for at least 2-3 weeks and up to a maximum of 6 weeks in order to achieve the desired clinical effect. In long standing depressive episodes, the latency of action can be prolonged for 8-10 weeks old, if not longer [20 21]. By adhering to the "Texas Algorithm" [22], defined on the basis of a study that evaluated the effectiveness of using an algorithm-driven treatment (ALGO) compared with treatment as usual (TAU) in depressed patients, it follows that a period of time as long as six months may have passed from the first drug prescribed in stage 1 to the treatment option in stage 4. If it was possible to develop criteria to facilitate a more rapid identification of an effective drug treatment, there would be obvious advantages: it would shorten the length of patient suffering and would reduce lost treatment time spent on ineffective drug treatments. It would also lead to more rapid optimization of drug therapy and would facilitate decisions on whether to increase or replace medication. Although some treatment guidelines indicate that the latency of action of antidepressants is shorter in non treatment resistant patients, the majority of them do not indicate any strategies aimed at optimizing treatment intervention; rather the advise is to wait and not make any drug changes before 4-6 weeks (Table I). These recommendations are based on the findings of placebo-controlled studies, where differences in response were only seen between the third and fourth week of treatment. This analysis led to the conclusion that an early response is mostly related to a placebo effect and a poor clinical improvement later.

By using this temporal pattern in the treatment of depression, other therapeutic treatments may be adversely effected, especially if symptoms such as lack of pleasure, initiative and interest persist. These residual symptoms represent an additional challenge to treatment. A drug perceived as ineffective may undermine a patient's motivation and therefore may cause early interruption of treatment, which carries not only an increased risk of suicide, but also of chronic illness and disability.

With recent neuro-imaging techniques, it now seems possible to identify those patients who are more likely to respond satisfactorily to antidepressant therapy. In a recent review [24] the authors highlight that in some MRI studies, larger volume in the hippocampus and the cingulate gyrus correlated with a greater tendency towards clinical remission.

Diffusion tensor imaging (DTI) is a magnetic resonance imaging tool where it is possible to construct three-dimensional biomedical images by exploiting the tendency of water molecules to move in an isotropic manner, meaning in one direction, due to the presence in biological tissues of barriers such as cell membranes. Using this technique, it has been demonstrated [25] that depressed patients who fail to obtain satisfactory clinical remission with SSRI therapy, have abnormalities in the white matter of the right amygdala while in contrast, the left amygdala and the hippocampus bilateral connections are not compromised. According to some authors [26], it is possible

Table I. When to consider changing drug therapy [22 23].

After 4 weeks, assessment of clinical response to pharmacological treatment, in order to optimize dosing.
Subsequent assessments at **8, 12, 16 weeks**.
Three possible treatment responses:
- Full Response
- Partial Response
- No Response

In the case of Full Response: continue drug therapy for al least 6 months
in the case of Partial Response: consider risk-benefit treatment factors
In the case of No Response: change of drug therapy recommended

using DTI to predict vulnerability to suicide behavior in euthymic patients with a history of depression.
A study investigating DTI in elderly depressed patients [27] showed the presence of reduced anisotropy in the white matter of various corticostriatal-limbic regions.
Some research has documented evidence of pharmacological efficacy within two weeks of treatment for several classes of antidepressants. In several studies the Stassen Group [28-30] have shown that an initial reduction of 20% of the Hamilton scale (within two weeks) is followed by a later clear and stable therapeutic response. Conversely, a lack of improvement in the first two weeks can be interpreted as a negative predictor of response. Also, by stratifying the sample of patients according to severity of symptoms at illness presentation, it was shown that response to drug therapy was related to the severity of depression (the more severe the symptoms at onset, the more consistent and rapid the extent of clinical improvement). Several other studies [31-36] have analyzed the predictive value of the initial response and it has been found that an improvement of the Hamilton scale of 20%, 25% or 30% after 2 weeks is a positive predictor of outcome after 6 weeks. Following on from these studies, Szegedi [37] introduced the concept of stable remission, defined as a 50% improvement of the Hamilton Scale Score, detected after 4 weeks and that persists after six weeks. Using the narrower criteria of stable remission, the percentage of patients obtain remission is reduced.
These results have been confirmed by further research conducted on over 6,000 patients [38 39] and included studies on tricyclic and tetracyclic antidepressants (TCAs: imipramine, amitriptyline, maprotiline), SSRIs (fluoxetine, paroxetine), NaSSA (mirtazapine), the reversible MAO-A inhibitor (moclobemide) and substance P antagonists. It has been postulated that antidepressants have a class effect and that no significant differences in efficacy exist among drugs in the same class, evidenced in part by number needed to treat analysis. This research further reinforces the idea that antidepressants have a class effect with regard to efficiency and latency of action.
It has been suggested that early response to treatment may be due to a placebo effect [40 41], for example, due to an implicit bias created by the increased attention paid by the investigators towards a patient during the early stages of the study. To help over come this problem, Gomeni [42] developed a statistical analysis that identifies placebo responders on the basis that their scores appear to be approximately double for a defined percentage of items of the Hamilton Scale.
Overall it can be assumed that if a patient fails to show any clinical response during the first two weeks of treatment, then the probability of obtaining an improvement is only 15% and this reduces further to 8% after three weeks. There is a small group of patients (on average 8%) where no improvement is detected after three weeks but they may still respond to drug therapy. In any event, the practice of treating patients for a long period of time in the absence of any initial improvement and without using a more assertive pharmacological treatment approach, needs to be questioned.
On the basis of these observations, a Working Group coordinated by Hans Stassen and supported by Jules Angst formulated the following guidelines:

Aim to prescribe an appropriate therapeutic drug dose within a short period of time;
If there is no sign of clinical improvement after 10 days, then:

- Increase the drug dose, or
- Choose an augmentation strategy

If after 3 weeks there is no improvement, then consider changing drug.

“Of course, these are only general guidelines and must be adapted to the clinical needs of the individual patient” (Jule Angst)”.

This advise appears to contrast with other recommendations on the prescription of antidepressants that promote a “start slow and go slow” approach and before being applied other important factors that influence drug prescribing must be considered, for example, illness severity, comorbidity, age, tolerance and treatment setting (inpatient or outpatient).
Other international research has shown that applying empirically based, systematic treatment algorithms, especially in an in-patient setting, can significantly reduce both the period of hospitalization and the number of drug prescriptions, resulting in greater patient satisfaction as well as professional satisfaction amongst colleagues (Conca 2007, unpublished results).
To achieve more optimal drug prescribing more attention should be paid to a drugs efficacy profile as well as to its side effect and safety profile, which in turn requires a more thorough understanding of the different classes of antidepressants. In terms of side effects, there are obvious differences between individual drugs: for example, the cardiotoxicity of TCA

and its significant anticholinergic side effects such as dry mouth, constipation and visual disturbance.
Informed and selective prescribing that takes into account both the side effect profile of a drug and the individual symptoms of the patient, leads to improved compliance and more effective treatment of the depressive disorder; residual symptoms such as lack of motivation, somnolence, ecc. may benefit from the combined intervention of prescribing an SSRI with a NDRI (e.g. bupropion).
Plasma drug monitoring or "Therapeutic Drug Monitoring" can optimize and individualize the different stages of treatment, provided it is used correctly [43]. It is a valuable tool has been used now for a number of years in everyday clinical practice for the optimization of pharmacotherapy and consists essentially of the measurement of plasma drug concentrations to inform eventual dose adjustments. For example, in the case of SSRIs, recent studies [44] using PET imaging of different regions of the brain, have shown that plasma concentrations have a positive correlation with the degree of receptor occupancy for the protein that transports serotonin. For example, 80% occupancy of striatal receptors is associated with a good therapeutic effect after 4 weeks of treatment with SSRIs. In the case of citalopram, a concentration of at least 50 ng/mL is required to obtain 80% striatal receptor occupancy.
With this type of study, it has been possible to identify a therapeutic range for each drug, below which the concentration of the molecule is considered insufficient to determine a satisfactory clinical response, while on the other hand in cases where the concentration exceeds the upper limit, the emergence of side effects is very likely.

Prediction of antidepressant response can be improved by a combination of early response assessment and plasma drug monitoring: in a multicenter open-label study on citalopram prescribed to 55 patients admitted with a diagnosis of major depression of moderate to severe severity [45], it was demonstrated that by using early response assessment to drug treatment, as measured on the HAM-D Scale (using a score of 24 as cut-off point) with plasma concentrations measured at day 7 (using a value of > 35 ng/ml as a cut off point), it was possible to predict antidepressant response at day 35 with a positive predictive value of 67% and a negative predictive value of 88%. A more recent similar study [46], assessed treatment with venlafaxine in a group of 88 patients and demonstrated that the predictive ability is even more reliable if plasma concentration measurements of the active metabolite (O-desmethyl-venlafaxine) are also considered.
In conclusion, there is sufficient evidence to show that the effect of action of antidepressants can be observed as early as 7-10 days of treatment. Therefore, onset of clinical response to antidepressant treatment is no longer just a matter of patience and can be influenced by prescribing practices. It becomes more challenging to identify effective treatment strategies when there is no response to treatment for which methodologically different research is needed. However, current reliable data and empirical experience have allowed clinicians to formulate valid treatment algorithms.
Finally, further understanding and research on the latency of action of antipsychotic drugs is also warranted [47].

Take home messages for psychiatric care

- The therapeutic effect of antidepressants is generally thought to take several weeks
- Several recent studies have however found evidence of an early treatment response, occurring within the first 2 weeks of antidepressant treatment
- Early treatment response, in association with Therapeutic Drug Monitoring, may predict treatment outcome

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AUGMENTATION OF PSYCHOPHARMACOLOGICAL TREATMENT WITH rTMS TO ACHIEVE CLINICAL HEALING: A CASE REPORT

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Summary
Objectives: Repetitive transcranial magnetic stimulation (rTMS) is useful in the treatment of recurrent major depressive disorder but its efficacy in elderly is still controversial. The present study aims to illustrate the outcome of a rTMS treatment in a 68 years old patient.
Materials and methods: rTMS therapy consisted of 30 sessions, six days a week. It was performed placing the butterfly coil over the left prefrontal cortex as defined by 5.5 cm anterior to the motor threshold (MT) site. The first treatment dose was fixed at 80% MT and slowly titrated to 100% within the fourth session; rTMS was applied at 10 Hz. A physiological examination and a clinical and neuropsychological assessment were carried out.
Results: The patient met the DSM-5 diagnostic criteria for recurrent major depressive disorder and generalized anxiety disorder. Her physical, neuropsychological and neurological examinations were normal. She showed an excellent response to the rTMS treatment.
Conclusions: rTMS in combination with pharmacotherapy resulted efficient in an old depressed patient who achieved a full functional recovery.

Key words: rTMS, depression, remission, elderly

Objectives

Repetitive transcranial magnetic stimulation (rTMS) proved to be safe and effective in treating the Major Depressive Disorder in patients who have not achieved improvement from prior antidepressant treatments. By contrast, its efficacy among the elderly (≥ 65 years) is unclear [1].
We report the case of a rTMS therapy in a 68 years old patient, in acute phase of illness.
Mrs A is an Italian housewife living in a country house with her husband. Second to last daughter in a large family, she graduated from primary school. During the young adulthood, she worked as farmer and had two children. In her family history, neoplasias occur but not psychiatric disorders, nor substance use disorders. She had a good health until she was 50, age of her first major depressive episode in association with marked anxiety symptoms. The first episode ended with a partial remission without full interepisode recovery after a SSRI medication. Since then, severe recurrent depressive episodes comorbid with generalized anxiety disorder occurred.
The most recent episode lasted 8 months and was still ongoing when Mrs A came to our Psychiatric Emergency Service.
At admission she looked sufficiently presentable, slow and brief in speech, with an anxious mimicry and decreased spontaneous gesticulation. She complained of a marked fatigue and reported abulia, anhedo-

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nia and lack of appetite, with a mild weight loss. She became easily upset and worried about everything happening around her. Her sleep, pharmacologically induced, was poorly restorative.
She had been taking for two months a stable psychotropic medication made up of venlafaxine 225mg/die, lithium 750 mg/die, risperidone 1.5 mg/die and lormetazepam 1.5 mg/die, obtaining a poor response. Previously, she had even taken multiple treatments with antidepressants (escitalopram, sertraline, trazodone, bupropion), mood stabilizers (lamotrigine and lithium), antipsychotics (quetiapine), benzodiazepines (lorazepam) and other psychotropic drugs, though remaining symptomatic.
Given the refractory nature of her symptoms, with the consent of Mrs A, TMS-naïve, we used a rTMS as augmentation to the pharmacological treatment.

Materials and Methods

The patient was assessed by psychiatrists using the Structured Clinical Interview for DSM-5-Clinical Version (SCID-5-CV) [2] and the Structured Clinical Interview for DSM-5-Personality Disorders (SCID-5-PD) [3]. Electroencephalogram (EEG), Brain Computed Tomography (Brain CT), blood/urine examinations and a neuropsychological assessment were carried out.
We started the rTMS therapy determining the motor threshold (MT, defined as the intensity over the motor hotspot at which 50% of pulses produced a discernible visual motor response in the patient's hand). Following the guidelines [4], we recorded the dose of rTMS administrated as percentage of the MT (80-100% MT).
rTMS therapy was performed using the MagVenture stimulator, MagPro R30, with the butterfly coil CoolDB80. The coil was placed over the left prefrontal cortex as defined by 5.5 cm anterior to MT site. The first treatment dose was fixed at 80% MT and slowly titrated to 100% within the fourth session; rTMS was applied at 10 Hz. The patient received a total of 30 treatments, six days a week. She rated the side effects (discomfort, pain at the point of stimulation, headache, anxiety, sleepiness, eye twitching, facial paraesthesia, epileptic seizures) of each stimulation on a Visual Analogue Scale (VAS). The side effects could be rated from 0 (None), to 2 (Very Mild), 4 (Mild), 6 (Moderate), 8 (Severe) and 10 (Very Severe).
A set of pre- and post- rTMS measures were collected and concerned: anxiety (*Hamilton Rating Scale for Anxiety* [5], HAM-A); depression (*Hamilton Rating Scale for Depression* [6], HAM-D; *Montgomery-Asberg Depression Rating Scale*[7], MADRS; *Beck Depression Inventory-II* [8], BDI-II; *Scala di Autovalutazione per la Depressione* [9], SAD); severity of psychiatric symptoms (*Brief Psychiatric Rating Scale - 4.0* [10], BPRS); improvement in clinical and social functioning (*Health of the Nation Outcome Scale - Rome* [11], HoNOS). The patient self-reported the quality of her life and her health and level of disability using respectively the World Health Organization Quality of Life - BREF [12] (WHOQoL) and the World Health Organization Disability Assessment Schedule 2.0 - 36 items [13] (WHODAS).

Results

Mrs A met the DSM-5 diagnostic criteria for recurrent major depressive disorder and generalized anxiety disorder. No personality disorder was diagnosed. Biochemistry, complete blood count, urine analysis, thyroid function tests, vitamin B12, folic acid levels were normal. We did not find any neuropsychological or neurological deficit.
After the therapy, Mrs A showed a decrease in the severity of symptoms and achieved the total remission within the 5th week of treatment. Specifically, the scales for depression and anxiety (HAM-D, HAM-A, MADRS) showed a decreased symptoms severity, from "Mild" to "Absent". The self-report scales for depression (SAD, BDI-II) exhibited an amelioration of the perceived symptoms from "Moderate" to "Absent". The severity of symptoms (BPRS) decreased from "Very Mild" to "Absent". At the beginning of rTMS treatment, the health and the psychosocial functioning (HoNOS) showed slight problems, which ceased to exist at the end of the therapy. The scores concerning the quality of life (WHOQoL) and the level of functioning (WHODAS) improved (see Table I).
The patient well tolerated the treatment reporting only "Sleepiness" (2.6/10; Mild - Very Mild) and "Eye twitching" (1.7/10; None - Very Mild) as side-effects of the rTMS treatments.
At the six-month follow-up, the good psychological functioning of Mrs A appeared preserved.

Conclusions

As it is known, the most important international guidelines regarding the management of depression[14] identify the full symptomatic remission and the return to the premorbid social functioning as a necessary goal to achieve. A partial remission should solicit the

Table I. Pre- and post-rTMS scores concerning clinical symptoms, social functioning, quality of life and level of disability.

	First session	After 6 TMS sessions	After 15 TMS sessions	After 30 TMS sessions
HAM-D	13			3
HAM-A	17			3
MADRS	18			2
BPRS	47			27
HoNOS	38			21
SAD	53	45	42	39
BDI-II	27	11	7	5
WHOQoL	61			90
WHODAS	73			37

HAM-D, Hamilton Rating Scale for Depression; HAM-A, Hamilton Rating Scale for Anxiety; MADRS, Montgomery - Asberg Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale - 4.0; HoNOS, Health of the nation Outcomes Scale - Rome; SAD, Scala di Autovalutazionedella-laDepressione; BDI-II, Beck Depression Inventory - II; WHOQoL, World Health Organization Quality of Life - BREF; WHODAS, World Health Organization Disability Assesment Schedule-2.0 36 items.

expert to revise the pharmacotherapy and the overall management of the intervention. Indeed, the persistence of mild or below threshold symptoms correlates with greater rates of disability and with the chronicization of the disorder, increasing the risk for relapses or recurrences and worsening the prognosis.

Until a few years ago, besides the pharmacotherapy, the psychotherapy and the electroconvulsive therapy (either alone or combined with psychotropics) were the only strategies for the treatment of depressive disorders. Currently, even in Italy, research is paving the way for a new physical treatment approach: rTMS.

Despite the high tolerability and safety of the rTMS in elderly, the literature often lacks evidence regarding its efficacy. However, no evidence found that rTMS is not recommended to treat the depression in elderly[15]. In our case, we chose an augmentation of pharmacotherapy with a rTMS therapy due to the poor response to several types of pharmacotherapy, the absence of a cortical atrophy (which may limit rTMS efficacy) and the considerable illness duration characterized by partial remissions and residual, albeit mild, symptoms. The rTMS in combination with pharmacotherapy demonstrated its efficacy in an old patient who achieved the complete recovery with a return to the previous level of functioning.

Conflict of interest

None.

Take home messages for psychiatric care

- rTMS can be used as an augmentation strategy to the pharmacotherapy when it achieves partial responses
- In our case, pharmacotherapy augmentation with rTMS proved its efficacy in an elderly patient

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EARLY RECOGNITION AND TREATMENT OF DELIRIUM USING THE CONFUSION ASSESSMENT METHOD FOR THE INTENSIVE CARE UNIT (CAM-ICU) IN A CARDIAC SURGICAL INTENSIVE CARE UNIT

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Summary

Introduction. Delirium is a complex cognitive disorder characterized by a disturbance in attention, awareness and cognition that are not better explained by another preexisting, neurocognitive disorder and that represents a direct physiological consequence of another medical condition, substance/medication intoxication or withdrawal, or exposure to a toxin. Delirium is highly prevalent in the cardiac surgical intensive care unit, as a result of the complexity of the surgical procedure and of the extracorporeal circulation. We report on the changes in the prevalence of delirium after the introduction in our Intensive Care Unit of a systematic assessment of delirium, via the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).

Materials and methods. We collected and analyzed data using an electronic medical records application (Digistat) and we compared the prevalence of delirium before and after the introduction of a systematic assessment in all admitted patients via the CAM-ICU. Our sample consisted of patients hospitalized in ICU after emergency or elective cardiac surgery in the periods from July 1, 2015 and December 31, 2015 (first group) and from July 1, 2016 and December 31, 2016 (second group). The diagnosis of delirium was formulated, in the first group, through a clinical evaluation by a specialist. In the second group, the diagnosis was formulated through the CAM-ICU.

Results. The first group consisted of 206 patients, of whom 86 (41.5%) showed clinical diagnosis of delirium. The second group consisted of 153 patients, of which only 17 (11.1%) showed a diagnosis of delirium. In our sample haloperidol was the most used drug. There was a low use of atypical antipsychotics and a high use of benzodiazepines. In the second group we showed less use of haloperidol and greater use of dexmedetomidine.

Conclusions. Our study shows a clear reduction in the diagnosis of delirium since the introduction of the CAM-ICU as a standard assessment for all our ICU patients. This reduced prevalence may be due to several factors including the early (i.e., before the development of a full-blown delirium syndrome) recognition and treatment of delirium symptoms. We also cannot exclude that the delirium diagnosis based on a clinical assessment overestimated, and/or that the diagnosis made via the CAM-ICU underestimated, the prevalence of delirium.

Key words: delirium, cardiac surgery; intensive care units; CAM-ICU; early recognition; psychopharmacological treatment

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Introduction

Delirium is a complex cognitive disorder characterized by a disturbance of consciousness with reduced ability to focus, sustain or shift attention. It is also characterized by decreased clarity of awareness of the environment and impaired cognitive functions such as memory deficit, disorientation, language disturbances and perceptual disorders, not justified by a preexisting or evolving dementia. Usually, clinical onset is acute and its course is short and fluctuating. Delirium is a direct consequence of a general medical condition, drug intoxication and/or withdrawal, toxicity exposure or a combination of these events. These deficits are not better explained by the presence of a neurocognitive disorder and do not occur in a context of severe reduction in vigilance, such as coma [1].

Other commonly associated symptoms include sleep disorders, disorders of the psychomotor activity and of emotionality. Patients can be either agitated (hyperactive/hyperkinetic delirium) and lethargic (hypoactive/hypokinetic delirium), and may have fluctuations between agitation and lethargy (mixed delirium) [2].

Delirium is a common postoperative complication, especially in the elderly. It is associated with increased mortality, post-traumatic stress disorder, longer length of hospital stay, extra nursing requirements, increased healthcare costs and substantial cognitive dysfunction for 1 year following surgery [3 4]. It is very common in critical patients and involves up to 80% of intubated patients in intensive care units (ICUs) [5].

Delirium is often a clinical manifestation of a general medical condition for which the treatment must aim at the correcting of the etiological factors that determine its onset. There is also a number of environmental and iatrogenic contributors to delirium such as prolonged immobilization, use of physical restraint, polypharmacy and use of sedative or opioid analgesic drugs, so attention should also be paid to identify and possibly correct these factors [2]. There is a subjective vulnerability correlated to the patient's medical condition, so the onset of delirium in a patient without comorbidity generally requires a number of significant insults, while in a fragile or compromised patient may be sufficient even a single insult of mild entity [6].

Delirium resulting from cardiac surgery is very frequent and represents a serious complication of patients hospitalized in cardiac surgery ICUs. The incidence of delirium after cardiac surgery is estimated to be 26-52% [4], with a significant percentage being hypoactive delirium [7].

The occurrence of delirium after cardiac surgery is associated with worse outcomes. These include increased rate of complications, prolonged duration of mechanical ventilation, prolonged length of stay in ICU and hospital, and increased medical expenses during hospitalization. Other negative outcomes are increased readmission rate, compromised long-term cognitive function, decreased physical ability and life quality, and elevated long-term mortality after hospital discharge [8 9].

The onset of delirium depends on both the patient's vulnerability and triggering factors related to surgery. To assess baseline vulnerability, the most widely used prediction rule for delirium after cardiac surgery was developed and validated by Rudolph et al. in 2009 and includes four items: prior stroke/transient ischemic attack, Geriatric Depression Scale > 4, abnormal albumin, and Mini-Mental State Examination (MMSE) score [10]. Intra-operative risk factors are related to the type and use of general versus local anesthesia, as well as the duration and type of surgery [11-12], reduction of cerebral perfusion linked to pressure imbalances [13], impaired cerebral auto-regulation and permeability of the blood-brain barrier [14].

Other predisposing risk factors include vision impairment, severe illness, cognitive impairment, and serum urea nitrogen: creatinine ratio of 18 or greater [15].

Vascular risk factors have also been strongly associated with development of delirium (tobacco use and vascular surgery), although it is unclear whether the increased risk is due to atherosclerotic burden or the surgical procedure itself [16].

Numerous pathophysiological mechanisms are involved in the genesis of delirium including increased inflammatory mediators and cortical changes [17], neurotransmittal imbalance [18], electrolyte and metabolic alterations [19], cerebral hemodynamic disorders [13] and genetic factors [20].

The development of delirium after cardiac surgery is associated with negative distance effects such as cognitive [21] and functional decline [22], reduced life expectancy [23], increased risk of stroke and mortality [24].

Currently there is no robust evidence demonstrating the effectiveness of various strategies to reduce the incidence of delirium in cardiac surgery[4] however early mobilization of patients is frequently considered to be a useful preventive intervention in non-cardiac surgical ICUs [25].

The use of preventive pharmacological therapy is controversial and usually is not recommended [4]. However, recent studies have shown the usefulness of prophylactic administration of haloperidol in patients

undergoing non-cardiac surgery [26] and risperidone in cardiac surgery patients [27]. Large randomized trials in cardiac surgical patients are needed to confirm the preventive efficacy of antipsychotic administration for the development of delirium [4]. A few studies show that the preoperative use of statins is protective against the development of delirium [28] while there is no evidence for the use of corticosteroids [29] and acetylcholinesterase inhibitors [30]. The choice of sedative therapy may affect the probability of delirium development: benzodiazepines and opioids are associated with increased risk [7], while dexmedetomidine may reduce the incidence and duration of cardiac post-surgery delirium [31].

Delirium treatment is based on the correction of triggering factors and causes removal, however, psycho-pharmacological therapy may be essential to control the symptoms and ensure patient safety. Although haloperidol has been considered the preferred agent for the treatment of delirium in critically ill patients, recent guidelines emphasize that the use of atypical antipsychotic agents may reduce the duration of delirium [2].

Although it's unclear how to manage patients with sub-syndromal delirium who are at high risk for progression to delirium, a recent study has shown the utility of low doses of risperidone (0.5 mg twice die) [32]. Knowing the incidence of delirium in this population can provide better pre- and postoperative planning to efficiently allocate resources and prevent the development of delirium, as well as improve postoperative management, with the least impact that this disorder can cause [33].

Without an appropriate diagnostic tool the diagnosis of delirium risks being not clinically recognized. The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most frequently employed reliable diagnostic tools [2].

Materials and methods

The purpose of the study was to evaluate the impact of the introduction of CAM-ICU on the diagnosis of delirium in a cardiac surgical ICU.

We considered patients hospitalized at the cardiac surgical ICU in the University Hospital of Siena, and compared the prevalence of delirium diagnosis before and after the introduction of CAM-ICU.

The CAM-ICU is a diagnostic scale for delirium diagnosis that is based on four features: 1) acute onset and fluctuating course, 2) inattention, 3) altered level of consciousness, 4) disorganized thinking. The patient is diagnosed as delirious (CAM-ICU positive) if he/she has both features 1 and 2 and either feature 3 or 4.

A 2012 meta-analysis considered nine studies evaluating CAM-ICU (969 patients) and concluded that this is an excellent diagnostic tool in critically ICU patients and has a global sensitivity of 80% and a specificity of 95.9% [34].

The third feature of the CAM-ICU requires the assessment of alteration of level of consciousness. This could be done by administering the Richmond Agitation Sedation Scale (RASS). Positive RASS scores denote positive or aggressive symptomatology ranging from +1 (mild restlessness) to +4 (dangerous agitation). The negative RASS scores differentiate between response to verbal commands (scores -1 to -3) and physical stimulus (scores -4 and -5). If the patient's RASS score is -4 or -5 or not arousable by verbal commands, no further evaluation for delirium is performed, because the patient is comatose and is unable to be assessed for delirium. For patients who are arousable (RASS scores of -3 and higher), delirium can be assessed with the ICD-SC or by the CAM-ICU. RASS has demonstrated high reliability and diagnostic validity for patients of various intensive medical, surgical, cardiac and neurosurgical fields [35].

This is a retrospective study on the prevalence of diagnosis of delirium in patients hospitalized in ICU after emergency or elective cardiac surgery before and after the introduction into day-to-day clinical practice of CAM-ICU.

The first group corresponds to the patients hospitalized in the period from July 1, 2015 and December 31, 2015 and the second group from July 1, 2016 and December 31, 2016.

In the first group, which corresponds to the period when CAM-ICU had not yet been introduced, the diagnosis of delirium was established by the clinical evaluation of the patient taking into account the presence of at least one of the following symptoms: confusion, agitation, delirium and depression. The choice to introduce among them the symptom of depression derives from the need to recognize hypoactive delirium, very common in intensive care units and often unrecognized for non-clinical presentation.

CAM-ICU has been introduced into the daily routine of cardiovascular surgery unit of our hospital from April 1, 2016. Since then, daily, three times a day, in morning, afternoon and night shifts, CAM-ICU was performed to each patient admitted by the nursing staff, after a one-year training period.

Results

The first group (1 July 2015 - December 31, 2015; pre-CAM) consisted of 206 patients with an average age of 67.4 (± 12.2) years, including 131 male and 75 female. The second group (1 July 2016 - December 31, 2016; post-CAM) consisted of 153 patients with an average age of 68.4 (± 12.5) years, of which 99 were males and 54 were females. The two groups, in addition to the number, did not differ significantly for the clinical features of the subjects (Figure 1). The most common types of patients were cardiac surgeries for valve or coronary intervention, or for double valve and coronary intervention. Other relatively frequent typologies of interventions were those related to ascending aorta and aortic arch. Another frequent type of intervention was the double valve intervention and the ascending aorta. Other cardiac surgery or chest surgery were less represented. Most of the interventions were in the election (87.9% in the first group and 86.2% in the second group). In the first group 17 interventions (8.2%) were in urgency and 8 (3.9%) in emergency; in the second group, urgent interventions were 8 (5.2%) and emergency 13 (8.5%). The diagnosis of delirium was assessed by clinical evaluation in 86 of 206 patients (41.5%) of the first group. In the second group, the diagnosis of delirium was postponed by the outcome of the CAM-ICU in 17 of 153 patients (11.1%) (Figure 2).

There were minimal differences between the two groups. The average duration of the hospitalization was 5.8 days for the first group and 6.6 days for the second group. The number of deaths was 9 for the first group and 16 for the second group.

In the first group there was a high use of haloperidol and benzodiazepines: 11 patients were treated with haloperidol and 12 with benzodiazepines and benzodiazepine analogues (lorazepam, alprazolam or zolpidem). There was a low use of new generation antipsychotics: only one patient was treated with quetiapine. There was a low use of dexmedetomidine (4 patients).

In the second group there was still a high use of benzodiazepines but lower use of haloperidol: 4 patients were treated with the latter and 12 with benzodiazepines and benzodiazepine analogues (lorazepam, alprazolam or zolpidem). Also in the second group there was a low use of new generation antipsychotics: only 2 patients were treated with quetiapine. Compared to the first group, there was a greater use of dexmedetomidine (8 patients).

No patients, both of the first and of the second group, had been treated with an antipsychotic other than haloperidol or quetiapine.

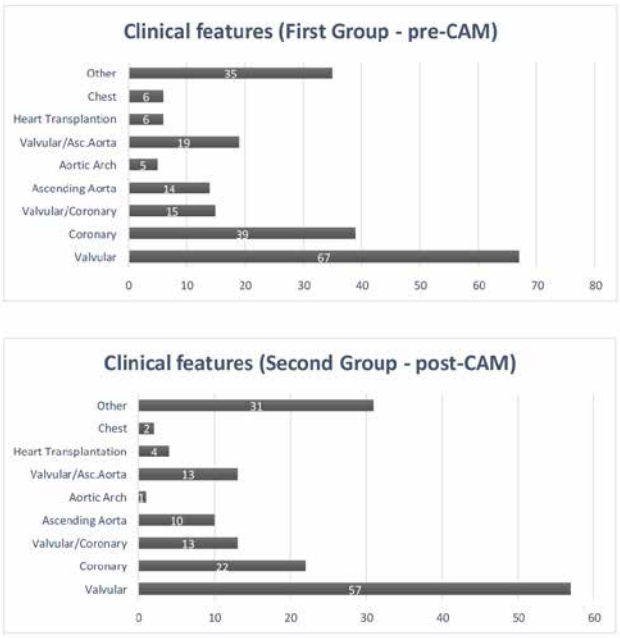

FIGURE 1.
Clinical features of the subjects.

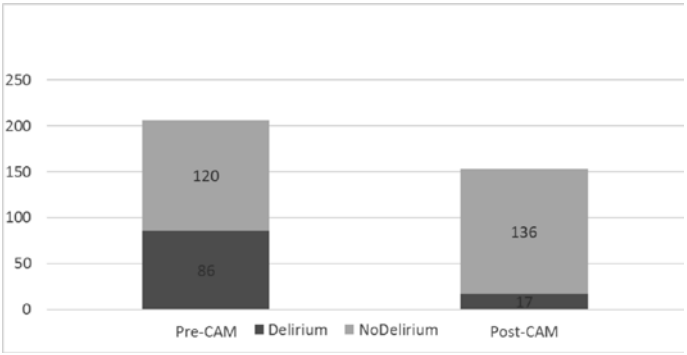

FIGURE 2.
Diagnosis of delirium in the two groups.

Discussion

The results of our study demonstrate a reduction in the diagnosis of delirium in cardiac surgery intensive care units after introduction into the clinical practice of CAM-ICU.

The only intervention that has shown, in randomized trials, to reduce the incidence of diagnosis and the duration of delirium symptoms in intensive care is early mobilization of patients [25] and recent guidelines recommend this intervention to reduce the incidence of delirium[2]. Other environmental and physical interventions, although have demonstrated to reduce the incidence of delirium in therapeutic settings other than intensive care [36], have not been adequately studied in

setting up the cardiovascular ICUs. A recent study on the effectiveness of communication between family members and patients in cardiac surgery has shown how the reassurance from the caregivers can reduce the incidence of postoperative delirium [37].

Evidence of the effectiveness of preventive drug therapy is controversial although some studies demonstrate the efficacy of low doses of risperidone in prophylaxis of delirium in patients undergoing cardiac surgery and haloperidol in prophylaxis of delirium in non-cardiac surgical intensive care [26 27]. However, recent guidelines do not recommend pharmacological interventions for the prevention of delirium in intensive care unit. The same guidelines underline the importance of the use of specific diagnostic scales such as CAM-ICU and ICDSC for delirium diagnosis [2].

The results of our study confirm the importance of CAM-ICU in the diagnosis of delirium and suggest its role in prevention.

We can assume that daily administration of CAM-ICU by nursing staff pays greater attention on the patient and allows early identification of the initial symptoms of delirium by allowing correction of triggers and appropriate therapy for both underlying causes and neuropsychiatric symptoms. The prevalence of delirium in the first group of patients in our study (41.5%) is very high but is in line with that one of other studies conducted within the same cure setting [6]. The prevalence of delirium in the second group of patients (11.1%) is very low, far below the average of other studies, although this does not result in a consequent reduction in the number of complications or mortality and in the duration of the hospitalization.

To our surprise, an earlier assessment and identification/diagnosis of delirium was not correlated with a shorter length of hospitalization or to a lower degree of mortality and complications. We argue that this could be due to the fact that other factors, such as the type of surgery that was performed, play a bigger role. Also, several conditions that contribute to delirium (e.g, electrolyte imbalance, anemia, etc) were likely addressed in both groups, independent on an early diagnosis of delirium.

In our sample, there was a high use of benzodiazepines, low use of atypical antipsychotics and, among other antipsychotics, preferential, if not exclusively, haloperidol use. These data contradict the suggestions of the latest guidelines on delirium in ICUs that conclude that there is no evidence for the efficacy of haloperidol in reducing delirium duration, while atypical antipsychotics may reduce the duration [2]. The same guidelines do not recommend the use of benzodiazepines in the treatment of delirium in intensive care unit except for cases of alcohol or sedatives withdrawal [2], while in our sample is highly utilized.

A difference that we found between the first and second group of patients was a less frequent use of haloperidol in the second group and greater use of dexmedetomidine in the latter. Dexmedetomidine is a selective agonist of $\alpha 2$ adrenergic receptors with sedative, anxiolytic and sympathetic properties [38]. In Italy, is approved for sedation of patients in intensive care units requiring a deeper level of sedation than awakening in response to verbal stimulation (corresponding to the score between 0 and -3 of the RASS). The main side effects are hypotension and bradycardia, while not leading to significant respiratory compromise [2]. Dexmedetomidine causes different sedation than classical sedatives, so patients are more easily awake and interactive [39].

Dexmedetomidine has also an analgesic effect that can reduce the need for opioids. There are many evidences that underline the importance of maintaining a light sedation level in intensive care patients and avoiding benzodiazepines among sedatives, in order to reduce the duration of assisted ventilation, the duration of the hospitalization and the incidence of delirium and cognitive decline. The use of dexmedetomidine as a sedative drug for the control of agitation may allow a reduced use of benzodiazepines and may favor a light sedation level, indirectly reducing the incidence of delirium [2]. Some evidence underlines the benefits of dexmedetomidine in comparison with benzodiazepines and propofol in reducing the risk of delirium after cardiac surgery [40]. We may also hypothesize that a greater use of dexmedetomidine in second group of our study, in addition to the introduction of CAM-ICU, may have contributed to a small reduction in the prevalence of delirium.

Although the results of the study favor a possible role of CAM-ICU in the prevention of delirium it can not be excluded that the reduced prevalence of delirium diagnosis in the second group of patients depends rather on the fact that clinical evaluation overestimates while the CAM-ICU underestimates the diagnosis of delirium.

Conclusions

The findings of this study confirm the importance of routine screening for the diagnosis of delirium in cardiac surgery through the use of accurate and reliable diagnostic tools such as CAM-ICU and suggest the possible positive impact on delirium prevention.

However, it is not possible to exclude with certainty that the reduced prevalence of delirium diagnosis after the introduction of CAM-ICU depends on the fact that the test diagnosis underestimates the diagnosis of delirium with respect to the clinical diagnosis.
Drug use data demonstrate that there is still no uniformity to the guidelines and how there is still a high use of benzodiazepines and a low use of different sedative medicines such as dexmedetomidine for control of agitation in cardiac surgery.

Conflict of interest

None.

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