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EVIDENCE-BASED PSYCHIATRIC CARE

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Contents

The closing of the Italian Forensic Hospitals: six months later. What we have learned and what we need
E. Sacchetti, C. Mencacci

Pharmacoepidemiology of bipolar disorder: a review
D. Dimellis, K.N. Fountoulakis

Symptoms of depression: "hot" and "cold" cognition
C. Gramaglia, F. Pietrini, P. Zeppegno

Mental health care needs of involuntarily admitted inpatients
M.S. Ritsner, Y. Ratner, R. Kurs, A. Grinshpoon

An update of the preclinical profile of lurasidone
M.A. Riva

Remission in depression after treatment: too obvious to clinicians, why so difficult to measure?
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CONTENTS

EDITORIAL

37 The closing of the Italian Forensic Hospitals: six months later. What we have learned and what we need
E. Sacchetti, C. Mencacci

REVIEWS

40 Pharmacoepidemiology of bipolar disorder: a review
D. Dimellis, K.N. Fountoulakis

48 Symptoms of depression: "hot" and "cold" cognition
C. Gramaglia, F. Pietrini, P. Zeppegno

59 Mental health care needs of involuntarily admitted inpatients
M.S. Ritsner, Y. Ratner, R. Kurs, A. Grinshpoon

67 An update of the preclinical profile of lurasidone
M.A. Riva

EDUCATIONAL

73 Remission in depression after treatment: too obvious to clinicians, why so difficult to measure?
C. Turrina, A. Vita, E. Sacchetti

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THE CLOSING OF THE ITALIAN FORENSIC HOSPITALS: SIX MONTHS LATER. WHAT WE HAVE LEARNED AND WHAT WE NEED

Emilio Sacchetti, Claudio Mencacci

Editors-in-Chief,
Evidence-Based Psychiatric Care
Presidents of the Italian Psychiatric Association (October 2012-2015)

In April 2015, after a long period of silence and hard work, law 81 (31 May 2014) ordering the closing of Italian Forensic Hospitals finally took effect. This law was made possible by the jointed effort not only of politicians, but also of the Italian Society of Psychiatry (Società Italiana di Psichiatria, SIP). It can be considered as a relatively unusual event in Italy that is, however, in line with other movements and psychiatric organisations that have endeavoured to combine two seemingly antithetical types of structures. On one hand, this guarantees the rights of each individual, independently of one's judicial status, to take full advantage of health services provided by the community. On the other, it guarantees the rights of a larger society to be protected from any criminal action, regardless of whether this is wholly or partly attributable to the altered mental state of the offender.

Six months after its introduction, we believe that it is possible to make an initial assessment on how well the law is working and on some additional needs that have arisen. For the first point, both good and bad aspects can be highlighted. One of the few good aspects is that concerns and alarmism about Forensic Hospitals discharging psychiatric offenders were decidedly unwarranted: the number of beds initially planned for Residential Services for the Execution of Security Measures (RSESM) have been demonstrated to be grossly excessive considering current needs. In the case that Departments of Mental Health (DMH) have the minimum requisites needed, in various regions in Italy, which have only partially adopted the new law, the entry points of patients into the DMH from a Forensic Hospital have proven to be generally achievable without substantial risks or changes to clinical routines of the DMH. From this initial experience, it can be concluded that the transfer of Forensic Hospital patients to community psychiatric services has been a positive experience overall. Thus, the law is not good only on paper, but it's also good and feasible in routine practice, given the availability of the necessary facilities.

There are, however, some pitfalls. The first is that the services available for patients discharged from a Forensic Hospital vary greatly: while various regions have more or less addressed the structural problem stipulated by law 81, other entities have continued as if nothing had changed. This patchy distribution of qualitative services and quantitative specialist interventions is unacceptable and can be considered discriminatory. Such a deadlock cannot be overcome by simple invitations and recom-

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mendations that have no real message: it will take a strong government stance that results in legal sanctions in the case of on-going inadequacies.
A second shortcoming, related to the first, is that too many regions, and consequently too many DMH, continue to focus debate on the RSESM, as if these structures were the key problem for overcoming Forensic Hospitals. This constitutes a slightly revised and somewhat incorrect version of the facts, and in reality the situation is much different. Moreover, as already mentioned, even if used correctly the valuable option of RSESM can only fulfil the needs of a minority of patients who are discharged from Forensic Hospitals. A third limitation is the fact that in spite of the repeated promises and assurances of Law 81, the majority of DMH have still not utilised the additional funding they were provided. During the closure phase of Forensic Hospitals, many DMH have been operating on much the same resources. However, as everyone knows, it is very hard to operate efficiently on a shoestring budget.
As for additional needs that have emerged, it must first of all be stressed that a small but not insignificant proportion of magistrates have continued to consider Acute Inpatient Psychiatric Services (AIPS) as a sort of surrogate for Forensic Hospitals. Paradoxically, there are judicial orders for psychiatric admission to AIPS for offenders awaiting psychiatric evaluation or for those whose medical conditions do not require psychiatric hospitalisation. In these situations, there is a clear conflict of interest between the magistrate who is ordering admission and the psychiatrist who, as a result of the magistrate's order, must carry out a task that is clearly custodian in nature. In addition, as a hospital bed is forcibly and improperly "occupied", admission of patients who have full rights during a phase of strong psychopathological decompensation must be deferred. Therefore, the formalisation of continuous and close dialogue between magistrates and psychiatrists, with a view to develop shared guidelines to address these issues and the diversity institutional roles, can no longer be postponed. The development of guidelines that are shared between magistrates and psychiatrists is also necessary to define the most appropriate placement of people who, whether or not previously discharged from a Forensic Hospital, commit new crimes because of their altered mental state. The choice to use former Forensic Hospitals, at least as long as they remain active in some way and provide psychiatric care in prisons or in structures related to the DMH, is not trivial and requires complex and careful planning that can substantially slow down the process of their final closure. The experience gained in the months immediately following the implementation of Law 81 has also clearly shown that some other issues initially placed at the periphery of the closure process of Forensic Hospitals are in reality central to the success of the operation. These include the overall organisation of psychiatric care in prison, redefinition of the concept of social danger and adequate review of psychiatric reports.
Considering organisation of care in prison a first premise seems necessary: even today, in many cases, psychiatric care in prison is implemented according to a dominant logic of psychiatrization of prison. In fact, psychiatrists working in correction facilities are often involved in tasks, such as mere psychological support, that are not theirs. They must work in a context that is unavoidably governed by rules that are frequently incompatible with those of standard psychiatric practice. These include things such as reduced safety standards, insufficient flexibility of guaranteed levels of monitoring, provision of most care by unqualified professional operators, lack of routinely available treatment options and reduced involvement of addiction services, despite the abnormally high rates of substance-related disorders among inmates. To overcome these problems, thorough screening of de novo psychiatric pathologies is needed to separate genuine cases from 'non-cases' represented by offenders who use psychiatry as a shortcut to obtain secondary benefits. Unfortunately, this is not the only priority for intervention. It is equally necessary to plan a complex set of other interventions that include, among other things, transfer of diagnostic and therapeutic guidelines used in DMH to prison life. In addition, interventions dedicated to specific themes such as psychomotor agitation and aggression directed towards oneself and/or others, stronger monitoring of adherence to therapy, the more systematic use of long-acting injectable drugs, inclusion of courses on psychiatric rehabilitation, a multidisciplinary approach to double diagnoses, ad hoc training of prison staff and adaptation of prison spaces to structural and safety standards typical of psychiatric care must be addressed.
In turn, redefining the concept of social danger is a prerequisite for the application of the law to overcome Forensic Hospitals. In fact, the attribution of a 'socially dangerous' label is sufficient to identify individuals intended for RSESM or, more in general, patients who require higher levels of surveillance. At the same time, however, it also appears increasingly clear that the current construct underlying the defi-

nition of social dangerousness is moving decisively towards strong and unfairly defensive psychiatry. Albeit with plenty of due caution, social dangerousness must be redefined by emphasising two key points. The first is that allocation of social danger for psychiatric reasons is not based on certainties, but rather on probabilistic forecasts that are often broad in nature and fairly transient as they are based on many external variables that cannot be fully controlled. The second is that the boundary between social danger inherent to a mental disorder and that associated with a "free choice delinquent" is often very thin, as indicated, for example, by the frequency with which the label of antisocial personality disorder is applied in the context of prison care.

These considerations introduce a third hot topic that requires urgent intervention: remodelling of psychiatric consultation. With adequate preparation and the right advice it is possible to fraudulently direct psychiatric consultation to one's own advantage. This affirmation becomes even more true as consultation moves away from the golden rule of a constant reference, almost spasmodic, to the medical history of the subject. Unfortunately, even today many technical consultants do not rely exclusively on clinical logic, and as a consequence draw conclusions that are highly inferential and not supported by evidence. The risk of inferential conclusions is even more remarkable given that much of the textbook guidance in routine use is obsolete, unconnected with the tools routinely used in clinical practice, and therefore unable to sufficiently support probative expert conclusions. Despite these obvious limitations, many judges rely too much on psychiatric consultations, giving them much more weight than they actually deserve. In addition, it is increasingly clear that some concepts typical of technical consultations, such as temporary mental disorder, as often cited by media sources, are events that are quite rare and therefore not applicable to the vast majority of cases.

For all these considerations, involvement between judges, lawyers, forensic doctors and psychiatrists seems to be, once again, the instrument of choice to ensure expert opinion that is genuinely respectful of clinical reality. This would be an achievement of substantial ethical value as it would finally allow a transition from justice that is sometimes based on medico-legal squabbles towards justice that is more fair. However, considering reform of psychiatric care in prison, the concept of social danger and specialised technical expertise are not just the structural core elements to ensure adequate closure of Forensic Hospitals, they are also the starting points for a broader process of revising the primary regulations governing clinical and medico-legal governance that can be applied to all offenders suffering from a specific mental disorder. The awareness that we have many irons in the fire should call for the opening of an exhaustive debate. *Evidence-based Psychiatric Care* will strongly encourage that this takes place.

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PHARMACOEPIDEMIOLOGY OF BIPOLAR DISORDER: A REVIEW

Abstract

Introduction: Pharmaco-epidemiological research by reflecting the use of drugs in real life situations, is crucial in exploring important public health issues related to psychotropic drug use, such as the medical and economic impact of unjustified extension of use, the identification of infrequent or delayed adverse effects, and the efficiency of new marketed products in naturalistic conditions. The scope of the current presentation is to review systematically the available data on the treatment of bipolar disorder.

Material and methods: A systematic MEDLINE search, concerning the treatment of bipolar disorder with 'mania', 'manic', 'bipolar', 'manic-depression', 'manic-depressive' with 'pharmacoepidemiology' or 'prescription' or 'prescription patterns' or 'therapeutic practice'as keywords, was performed.

Results: The literature suggests that the treatment of bipolar disorder is driven by symptomatology and falls short of the existing guidelines. Regarding acute mania, the use of antipsychotics is preferred over lithium or anticonvulsants either as monotherapy or as combination treatment. The data about bipolar depression are scarce and limited although the use of antidepressants is more common in everyday practice than the guidelines advice. Finally, as for the maintenance phase, the use of lithium seems to vary worldwide, whereas the use of antipsychotics is common, especially for those patients with psychotic features or with more complicated course. Astonishingly, 25-50% of bipolar patients are, cross-sectionally, under antidepressants. Overall, less than 40% of patients are on monotherapy and the percentage is falling, while polypharmacy seems to dominate the pharmacotherapy of bipolar disorder, with up to 50% of patients receiving 3 or more psychoactive drugs at the same time.

Conclusions: Available data confirm that clinicians do not follow, at least strictly, the proposed guidelines. On the other hand, the effectiveness of the available treatments lies far from ideal, a fact that offers a ground for combinations, despite their increased burden of side effects. There is abundant room for further progress in determining more "clinician friendly" guidelines and treatment choices.

Key words: bipolar disorder, aniconvulsants, antidepressants, antipsychotics, lithium, mood stabilizers, treatment, pharmacoepidemiology

Introduction

Traditionally the understanding of bipolar disorder (BD) suggested that it is an episodic illness with a return to premorbid level of functioning between the episodes and a favourable outcome in comparison to schizophrenia [1]. Today we know that this is not always the case [2] and the Kraepelinian concept largely corresponds to BD-I. Frequently there is a delay of several years before the correct diagnosis is being put.

Delaying correct diagnosis has profound implications concerning the choice of treatment and its overall efficacy, as treatment differs according to diagnosis. Consequently, treatment outcome might be suboptimal. This outcome is, also, strongly related to younger age of onset and to alcohol and substance abuse. Another important issue is the associated with mood disorders suicidality. Finally, regarding the resulting, overall

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disability BD has been ranked amongst the 10 most disabling medical conditions world-wide by the World Health Organization (WHO) [3].

The treatment of bipolar illness is not only affected by the correct diagnosis but it is, also, complex and full of caveats for the clinician [4-7]. It is true that the earlier studies tended to suggest a high and global effectiveness for older agents on all facets of BD and a high prevalence of switching with antidepressants constructing the widespread concept of 'class effect'. Neither conclusion is confirmed by newer studies and the recent data suggest that it is doubtful any class effect is present, maybe except from the efficacy of antipsychotics against acute mania.

From a clinical point of view, depression and the maintenance phase seem to be more important since effective treatments are much fewer in comparison to acute mania. In this frame, while evidence based medicine seems to dominate medical scientific thinking in the last decades, this is not true for the wider clinical practice, mainly because the evidence is limited and hard to interpret and to carry in everyday practice. On the other hand, it is highly likely that a significant number of bipolar patients worldwide are not recieving proper treatment simply because continued scientific training and reading is inadequate. Focused educational intervention might be nessessary to change this attitude.

Pharmaco-epidemiological research is crucial in order to explore important public health issues related to psychotropic drug use, such as the medical and economic impact of unjustified extension of use, the identification of infrequent or delayed adverse effects, and the efficiency of new marketed products in naturalistic conditions [8]. The scope of the current review was to explore the pharmaco-epidemiological data of BD the way the average psychiatrist treats patients.

Material and Method

The MEDLINE was searched in order to locate papers with concerning the pharmacoepidemiology of BD. The search strategy inlcuded the combination of each one of the key words 'mania', 'manic', 'bipolar', 'manic-depression', 'manic-depressive' with 'pharmacoepidemiology' or 'prescription' or 'prescription patterns' or 'therapeutic practice'. The search strategy was augmented through the inspection of reference lists of relevant review articles. Eligible articles included original studies in English.

Two investigators (KNF and DD) independently reviewed articles for eligibility. If either deemed an article as potentially eligible based on title/abstract review, then a full-text review was performed. The references of retrieved articles were hand-searched for further relevant articles and other relevant data were included. Final decisions regarding the eligibility were made by consensus following the full-text review.

Acute mania

There are not much data on the real world clinical practice concerning the pharmacotherapy of acute bipolar mania. The first studies revealed a cautionary attitude towards lithium and antiepileptics during the acute manic phase and a favor of typical antipsychotics. The review of therapeutic practices from two psychiatric care centres in Germany between 1975 und 1991 revealed that neuroleptics were preferred over lithium and carbamazepine. Combinations of more potent antipsychotics with more sedative neuroleptics were usual [9]. In the 1980s a decrease in the frequency of neuroleptic monotherapy and an increased proportion of combined treatments with lithium or carbamazepine were observed, however lithium and antiepileptics were still not widely accepted 10. On the contrary, in Japan it was reported that lithium was the most popular treatment for bipolar mania [11].

More recent studies, after the introduction of atypical antipsychotics showed a resistance of these attitudes. The study of treatment patterns at the University department of Psychiatry in Vienna Austria from 1997 to 1999 revealed that international guidelines were not included in daily practice with regard to the usage pattern of atypical antipsychotics versus typical neuroleptics or concerning monotherapy with a mood stabilizer as first-line treatment for acute mania as polypharmacy was the predominant treatment scheme [12]. Before the establishment of second generation antipsychotics as effective antimanic agents, it has been reported that overall, 84.7% of bipolar patients received typical antipsychotic agents; 53.8% was on monotherapy and 47.4% in combination with a mood stabilizer [13]. The evaluation of treatment practices against acute mania in a private psychiatric hospital in Brazil, from 1996 to 2000 revealed that the most frequent agents used were antipsychotics (83.3%) followed by lithium (71.5%), carbamazepine (34.8%), valproate (9.4%) and ECT (33.2%). There was a frequent concomitant use of ECT with lithium (72.3%) [14]. An epidemiologic study from the US on first-admission bipolar patients with psychotic features suggested that more patients received antipsychotics (80.0%) than lithium or antiepileptics (52.3%)

at discharge. After two years, 44.6% reported using no medications while 19.4% and 38.8% were taking antipsychotics and antimanics, respectively [15].

Acute bipolar depression

Pharmacoepidemiological data are rare concerning the treatment of bipolar depression. An unpublished poster presentation from Japan reported that the Japanesse psychiatrists were divided between antidepressants and mood stabilizers on the treatment of bipolar depression [11]. An old study from the '90s utilized the pharmacy records of the McLean Hospital from 1987 to 1993 and reported that 3829 bipolar depressive inpatients had received tricyclic antidepressants, 2981 fluoxetine, 2603 trazodone, 809 bupropion, 743 monoamine oxidase inhibitors, 592 stimulants, 588 sertraline, 48 paroxetine, and 894 ECT [16].

Maintenance treatment

There are several pharmacoepidemiological studies exploring prescription patterns, especially concerning lithium, monotherapy *vs* combination therapy, the discrepancy between official treatment guidelines and clinical practice as well as the change in patterns with the introduction of atypical antipsychotics and SSRIs. The studies cover a broad spectrum of data bases and come from the US [17-27], Denmark, Norway and Sweden [28 29], the Netherlands [30] Spain [31], Hungary [32], and the UK [33 34].

The prevalence of lithium treatment for the years 2005-6 was estimated between 17 and 25 per 10,000 persons of the general population in Denmark, Norway and Sweden [29]. In the Netherlands, during 1996-2005, the use was significantly lower with 9.5-12 per 10,000 persons [30]. USA data from the Oregon Medicaid during 1998-2003 reported that 25% of bipolar patients were receiving lithium, which corresponds to 12.5-25 persons per 10,000 [18]. Data from the clinical database of the Palo Alto Veterans Affairs Medical Center for the years 1989-95 suggested that there was a decline in the rate of lithium monotherapy for treatment of bipolar affective disorder from 84% to 43% (43 per 10,000 persons) [26]. The STEP-BD data suggest that lithium was prescribed to 37.8% of younger patients compared with only 29.5% of older participants [19]. The 2002-2003 U.S. national MarketScan database data suggest that 8% of bipolar patients were on lithium with almost half of them being on monotherapy which was more long-standing than with other stabilizers [21]. Thus US pharmacoepidemiological data for lithium vary widely (from 8-50 per 10,000) probably depending on sampling while also race seems to play a role with blacks being significantly less likely to receive lithium [22]. Overall pharmacoepidemiological data from around the world suggest that lithium use varies from 8-50 per 10,000 persons of the general population and the reason for this remains to be clarified [31 33]. Data from Germany suggested that the majority of patients (54.3%) were under monotherapy while 39.3% of patients were receiving two agents, and 6.6% three agents. Antidepressants (64.1%) were the most common combination medications [35].

The frequency of combination therapy is another question. According to most RCTs almost half of patients do not respond to monotherapy treatment during the acute manic phase. Thus it is expected that combination treatment will be widely spread in everyday clinical practice [17 32]. The 2002-2003 U.S. national MarketScan research databases suggest that only 44% of patients were receiving monotherapy. Median time to adding another psychotropic was 2.5-times less than median time to changing the initial treatment (16.4 compared with 40.9 weeks), and stopping was rare. An increase in the number of psychotropic medications prescribed across years 1996-2006 has been recorded; visits with 2 or more medications increased from 42.6% in 1996-1997 to 59.8% in 2005-2006; visits with 3 or more medications increased from 16.9% to 33.2%. Prescription for 2 or more antidepressants, antipsychotics, sedative-hypnotics, and antidepressant-antipsychotic combinations, but not other combinations, significantly increased across survey years. There was no increase in prescription of mood stabilizer combinations [27]. Intake treatment data for the first 500 patients in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (1998 to 1999) revealed that only 11 % of patients were treated with standard mood stabilizer monotherapy [23], while latter it has been reported that on average, participants who reached a recovered status took 2.05 medications with no difference between age groups [19].

Suicidality is reported to relate to more complex treatment patterns [17] while in comparison to lithium treated, divalproex treated patients were reported to had had 1.5 and gabapentin 2.6 hazard ratio of commiting suicide while data for carbamazepine are not available [18].

The above suggest that only 10-40% of patients are on monotherapy and the percentage is falling; on the contrary polypharmacy is increasingly becoming eve-

ryday practice with 25-50% receiving three or more agents simultaneously, with a trend towards increasing number of agents.

An old dilemma was also the US *vs* Europe approach to the treatment of BD meaning the preferable use of lithium and anticonvulsants *vs* antipsychotics and antidepressants; this dilemma was weakend with the recent approval of atypical antipsychotics for the treatment of BD. However even before that approval, the pharmacoepidemiological data suggest that a significant proportion of patients were under antipsychotics, including typical.

US data suggest that in privately insured individuals aged 18-64 during the years 1994-1998, first-generation antipsychotics were used by 16.4% of patients and second-generation agents by 12.4%. Patients starting on antipsychotics tended to stay with them for 12 months or longer, while patients starting on anticonvulsants were more likely to stop therapy or to switch to another medication class [24]. Also a subset of data from a larger voluntary registry on non-hospitalized subjects with bipolar I disorder in 1995/96 suggested that nearly one-third of all patients were receiving antipsychotic agents (66% typical) [25]. The 2002-2003 U.S. national MarketScan research databases suggest that mood stabilizers were more frequently prescribed as first drug than antipsychotics (25% *vs* 11%) with 17% anticonvulsants and 8% lithium. Overall half of patients were on lithium and one third on antipsychotics and the median weeks until therapy was changed in any way was 29 weeks for lithium *vs* 13 for antipsychotics [21]. Intake treatment data for the first 500 patients in the STEP-BD study (1998 to 1999) revealed that standard mood stabilizers (lithium, valproate, or carbamazepine) were the most commonly prescribed class of drugs that participants were taking at intake (71.9 %), followed by novel anticonvulsants (31.8%), *vs* second-generation neuroleptics (27.2%) [23]. The UK data from the case note review of the pharmacotherapy from a specified South London sector of a National Health Service Trust suggested that half of the patients were on mood-stabilizers (usually lithium) and their use was associated with female gender and multiple admissions. Antipsychotics were more commonly used in patients with psychotic features and multiple manic episodes [34]. The case note review of North-East of England suggested antipsychotic use was almost equally split between typical and atypical drugs [33]. The Prescribing Observatory for Mental Health reviewed data from 35 National Health Service Trusts on 2776 patients with a diagnosis of affective illness. These data suggested that 10% of patients had lithium levels below the therapeutic range and that co-prescribing of lithim plus antipsychotics was common (57%) [36].

US data suggest that race also influences with blacks being less likely to receive lithium and significantly more likely to receive first-generation antipsychotics and any antipsychotic and less likely lithium and SSRIs [22].

A similar picture was found concerning antidepressants. The US data from non-hospitalized subjects with bipolar I disorder in 1995/96 suggested that more than half of all subjects were receiving concomitant antidepressants, of whom nearly 50% received the SSRI antidepressants and nearly 25% received buproprion [25]. The data from the 2002-2003 U.S. national MarketScan research databases data suggest that the most commonly prescribed first drug class was antidepressants (50% of patients) [21]. Intake treatment data for the first 500 patients in the STEP-BD study (1998 to 1999) revealed that the second most common class of agents was antidepressants (40.6 %) [23].

In the Netherlands the search of prescription patterns during 1996-2005 revealed a significant decrease in the use of tricyclic antidepressants, which, however were still in wide use [30]. A small Hungarian study reported that 35% of patients was on antidepressants and more than half of them on SSRI, which implies a sustained wide use of tricyclics [32]. The UK data from the case note review of North-East of England suggested that 23% of patients were on antidepressants; 11% of them were not prescribed a mood stabilizer and 43% of antidepressants prescribed were tricyclics [33], while the case note review of South London National Health Service Trust on the contrary reported that antidepressants were rarely prescribed alone [34].

Taken the above together, it seems that depending on the sample, 25-50% of bipolar patients are cross-sectionally under antidepressants, with almost half of them receiving tricyclics, sometimes without concomitant antimanic agents.

Discussion

The earlier studies suggest a high and global effectiveness for older agents on all facets of BD and a high prevalence of switching with antidepressants, which were not confirmed by newer studies. On the other hand, these old agents are considered to be the 'gold standard' and are used as comparators in randomized trials of newer drugs. Since some of these studies are superiority ones, the literature could include data that might be misleading concerning the

older agents and in favour of newer drugs. This is a bias inherent in the literature and it should be taken into consideration when interpreting the data. Another possible source of bias is the fact that today the use of lithium is much more widespread and patients with a favorable response are unwilling to participate in a study with the risk of dropping it. This fact might have led to the inclusion of a disproportionally percentage of refractory to lithium patients and also of patients suffering from milder symptomatology in most recent studies [37]. Another problem with recent trials is the high dropout rate that limits the generalizability of the results [38 39]. Those high attrition rates, however, may be in part attributable to higher ethical standards in modern studies.

On the other hand, it is widely accepted that lithium possesses a specific anti-suicidal effect [40-48] and this is supported by a systematic review [49], although there is some concern that there was an over-interpretation of data [50]. However the STEP-BD study results do not support this [51]. Lithium is more effective against mania and to a lesser degree against depression [40 52-54]. Some patients appear to develop a tolerance to lithium after several years of successful use; a lithium discontinuation-induced refractoriness is also reported in up to 15% of patients [55]. Patients with an episodic course with euthymic intervals, and the absence of rapid cycling may respond better to lithium [56-60]. It is unclear whether after plolonged treatment it exerts a neuroprotective or a neurotoxic effect [61] and its mode of action is unclear [62]. Adverse effects are to be expected during lithium therapy [63].

Only antipsychotics possess such a 'class effect' against acute mania, while it is clear that there is no 'class effect' of any kind concerning either antiepileptics or antidepressants. This is of high importance since it seems that most clinicians consider that such an effect is the rule rather than the exception. If this proves to be so, then many patients worldwide might receive inappropriate treatment.

Regarding entipepileptics both valproate and carbamazepine are approved by the FDA for the treatment of acute manic episodes. A different case is lamotrigine, which is approved only for maintenance treatment. Several experts and drug licensing authorities do not consider its data strong enough [64] to merit an acute bipolar depression label. In spite of this, response rates against depression are reported to be 50% and are double than those observed under placebo [65]. The U.S. Food and Drug Administration (FDA) has already approved 6 SGAs for the treatment of acute mania: olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole and asenapine. These drugs are also approved for the treatment of mania in most European countries. Quetiapine and Lurasidone currently are the only SGAs with an FDA indication against bipolar depression as monotherapy. Olanzapine is approved for mania and the maintenance phase, and OFC for depression, while aripiprazole is also approved for mania and the maintenance phase. First generation (typical) antipsychotics (FGAs) and especially haloperidol, were used for long especially for the treatment of acute mania and were considered to act faster than mood stabilizers, however the anecdotal clinical impression may psychiatrists have is that they induce depression was recently supported by two studies [66]. A recent review suggests that the magnitude of improvement was similar whether the SGAs were utilized as monotherapy or adjunctive therapy [67]. If the patient has a life history of predominant manic or mixed episodes with rare and short depressive episodes, the administration of an SGA alone could be enough to control the disorder [68].

The most controversial of all classes of agents used in BD is antidepressants. Fluoxetine is the only antidepressant with official approval by the FDA for use in BD, not as monotherapy, but in combination with olanzapine. The use and usefulness of antidepressant agents in BD is controversial. Even their true effectiveness has been questioned, in spite of the randomized studies and the conclusion of a recent systematic review [69]. Guidelines suggest their cautious use and always in combination with an antimanic agent [6]. This is because antidepressants are believed to induce switching to mania or hypomania [70-73] mixed episodes [74] and rapid cycling, while research suggests that the use of antimanic agents might protect from such an effect [75]. Earlier studies pointed this problem especially with tricyclics [76-78] **44** however this may not be exactly the case with newer compounds. Some authors suggest the true rate of switching is rather low [79-81], while most studies reporting such an effect suffer from serious methodological problems while a strong publication bias is likely to be present [82]. The recent STEP-BD study produced equivocal results but generally they do not support the concept that antidepressant use worsens the course of the illness [83-86].

Beyond this reasonable doubt concerning the dangers of antidepressant use, the general concept is that dual action agents (TCAs or SNRIs) may be more potent in increasing the risk for switching to mania or hypomania [70] and to suicide [87 88]. Bipolar

II patients could be at the highest risk [89]. The concomitant use of an antimanic agent (atypical antipsychotic or anticonvulsant) may protect against switching or mixed symptoms, but this does not happen always [70 90]. However, on the contrary, in patients more prone to experience depressive episodes the continuation treatment with antidepressants might be beneficial [91-93].

Most authors agree that after the second episode of bipolar illness, long-term treatment is necessary, but this may still be too conservative, with most patients actually benefiting from early lifelong therapy. This treatment is based on the use of lithium, aripiprazole, olanzapine or olanzapine-fluoxetine combination, quetiapine and lamotrigine either as monotherapy or in combination. Traditional choices like valproate do not have sufficient scientific support. The choice depends largely on the longitudinal course of the illness and the predominant polarity of the episodes as well as previous response to a specific agent. Although it has been claimed that maintenance treatment should last at least 2 years after an episode or 5 years if the patient has risk factors for relapse [94], in clinical practice it is better to plan for lifetime treatment unless contraindications or specific issues would go against it.

Conclusively, pharmaco-epidemiological studies revealed early that clinicians do not follow treatment recommendations made by experts and it is unlikely they base their judgement on research data [8]. This was stricking in the case of first generation antipsychotics *vs* antiepileptics [95] as well as concerning the use of antidepressants [16]. Esprecially, regarding antidepressants, literature suggest that they represent the most commonly prescribed class of psychotropics in BD with 25-50% receiving one [21 25]. Furthermore, combination seems to be the preffered treatment choice over monotherapy [23 17]. The general picture from pharmaco-epidemiological studies is that in everyday ordinary care, the treatment of bipolar patients is often driven by symptoms and falls short of the existing practice guidelines [34].

Take home messages for psychiatric care

- Literature overall, and especially regarding bipolar depression, is scarce and limited
- Symptomatology rather, than guidelines, drives the choice of treatment thus clinicians do not follow strictly the proposed guidelines
- Acute mania: Antipsychotics are preferred over mood stabilizers-anticonvulsants
- Acute bipolar depression: The use of antidepressants is more common than the guidelines suggest
- Maintenance phase: Polypharmacy dominates monotherapy. The use of lithium varies while as much as 50% of bipolar patients are on antidepressants

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SYMPTOMS OF DEPRESSION: "HOT" AND "COLD" COGNITION

Abstract

Objectives: The central role of cognitive deficits in depression is well established and represents a primary mediator of the negative consequences of this disorder in both human and economic terms. The aim of the present review is to provide an up-to-date overview of current knowledge on the cognitive aspects of depression with particular focus on their clinical-therapeutic role.

Materials and methods: English language and peer-reviewed publications were obtained by searching PubMed/Medline database using the keywords "depression" or "depressive" paired with "cognition", "cognitive", "cold", "hot", "deficit", and "executive function".

Results: Recent studies have identified different cognitive systems that, when dysfunctional, play a crucial role in the onset and maintenance of depression: cognitive functions that are independent of emotional state ("cold" cognition) and cognitive regulation of emotional states ("hot" cognition). These systems develop an interaction between cognition and affectivity termed "affective cognition", which is frequently dysfunctional in individuals with depression.

Conclusions: cognitive symptoms are increasingly the focus of clinical and scientific debate on depression, not only for their diagnostic utility, but also for their importance in the prognosis, therapy and rehabilitation of this disorder.

Key words: depression, deficit, cognitive, affectivity, cognition, bias, antidepressants

Introduction

Depression is a severe, chronic syndrome with significant impact on functioning and quality of life, and is the leading cause of disability worldwide [1 2]. Major depression varies considerably in terms of clinical presentation and response to therapy, and includes a broad range of different phenotypes [3-6]. However, available literature indicates that cognitive impairment associated with depression is the main driver of negative consequences in both human and economic terms [7 8].

The key role of cognitive dysfunction in depression has been amply demonstrated [9-12], which is reinforced by current diagnostic systems [13]. The Diagnostic and Statistical Manual of Mental Disorders, 5th Ed. (DMS-5), in fact, includes cognitive dysfunction as a diagnostic criterion of major depression by itself (criterion 8: diminished ability to think or concentrate, or indecisiveness, nearly every day) and as a component of other cardinal symptoms (Criterion 2: markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day; Criterion 5: psychomotor agitation or retardation nearly every day) [13].

Cognitive depressive symptomology is a subject of clinical and scientific debate not only for its diagnostic value, but also for its importance in prognosis, therapy and rehabilitation [14]. Indeed, the available evidence indicates that the cognitive dimension of major depression is one of the main indicators of vulnerability [15], clinical course [16], response to therapy (both antidepressant [17 18] and psychotherapy [19]) and functional recovery [7].

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In regard to depression treatment, for example, some antidepressants have a demonstrated efficacy not only on the affective aspects of major depression, but also on cognitive depressive symptoms (especially those involving executive functions and emotional processing) [20-22]. In particular, current research has focused on selective serotonin reuptake inhibitors (SSRI) and selective norepinephrine reuptake inhibitors (SNRI), with the latter showing superiority over the former in terms of efficacy on cognitive aspects [23 24]. Other non-pharmacological treatments such as cognitive-behavioural therapy and cognitive remediation are also considered promising approaches in the treatment of major depression [21].

Over the last two decades [25], several cognitive systems have been identified that play a crucial role in the onset and maintenance of depression: executive cognitive functions that are independent of the emotional state ("cold" cognition which functions in control of cognition) and affective cognitive processes ("hot" cognition which functions in elaboration of emotionally-relevant stimuli) [10 26]. These two systems develop an interaction between cognition and affectivity ("affective cognition") that guides thought and behaviour in the response to emotionally relevant stimuli[12 26-28]. It is this interaction that appears dysfunctional in subjects with depression [29].

The aim of the present review is to provide up-to-date information on the cognitive aspects of depression, with focus on the alterations of executive functions ("cold" cognition) and of the cognitive regulation of emotions ("hot" cognition).

Materials and methods

A review of the literature was performed searching PubMed and electronic data base through July 2015 for studies published in English at any time prior to the search date. Searches were conducted using the keywords "depression" or "depressive" paired with "cognition", "cognitive", "cold", "hot", "deficit", and "executive function" (e.g. "Depression/diagnosis"[Mesh] OR "Depression/physiopathology"[Mesh] OR "Depression/psychology"[Mesh] AND "cognition"[Mesh]). An initial screening was conducted by examining titles to eliminate studies that clearly did not meet the inclusion criteria. Searches excluded bipolar, psychosis, stroke, Parkinson's disease, Alzheimer's disease, and post-partum depression. The remaining abstracts were reviewed to identify studies, systematic reviews, and meta-analyses evaluating cognition in patients with depression. Selection criteria were: original neuropsychological investigations with a healthy control group and use of tasks investigating cognitive function, emotional processing, or reward/punishment processing or systematic reviews and meta-analyses. If an article appeared likely to meet the inclusion criteria the full text was obtained. In addition, the reference lists of included articles, and articles citing included articles, were screened for any studies missed in the database search process. We focused on studies reported in the past 15 years but also included commonly referenced and highly regarded older publications. Whenever the data obtained by a single study were later included in a meta-analysis we choose to refer to the results of the meta-analysis rather than to the results of the original study. Review articles and book chapters are cited to provide readers with more details and additional references.

"Cold" cognition in depression

Executive functions, classically belonging to "cold cognition" or independent of affectivity, are represented by systems with inhibitory action (suppression of some answers to give priority to others), information management (working memory) and adaptation to external requests (modulation of response and addressing attention) [30]. The correct combination of these systems represents the basis for organisation of higher order executive functions such as problem solving and planning behavioural responses [25].

In theory, "cold" cognitive functions can be evaluated with tests that involve emotionally and motivationally neutral stimuli. On the basis of this principle, over the years, a series of neuropsychological instruments have been developed that include the Digit Symbol Substitution Test (DSST), the California Verbal Learning Test (CVLT), the Wisconsin Card Sorting Test (WCST), the Trail-Making Test (TMT) and the Stroop Colour-Word Interference Test (SCWT) [11]. These instruments have been used in a number of neuropsychological studies to investigate the principal domains of "cold" cognition in depression (including working memory, selective attention, response inhibition, cognitive flexibility, motor inhibition and verbal fluency), which have highlighted that there are important deficits in these functions in depression [9].

The results of the present review on cold cognition in depression are summarized in Table I. In two recent meta-analyses of the available neuropsychological studies, the degree of compromise of cognitive function in depression was demonstrated to have little

correlation with the severity of symptoms, underlining the importance of these deficits even in the subclinical phases and in remission [35 42].

Through neuropsychological research and the recent availability of advanced imaging techniques, the attention on the cognitive symptoms of depression has focused on the neural basis of these dysfunctions [29 46]. Neuroimaging studies of "cold" cognitive processes have investigated a series of domains (including working memory, verbal fluency, inhibition of response and selective attention) using various types of stimulation or tasks (Stroop task, Go/No-Go, continuous performance task, etc.) and functional imaging techniques [47]. The results of this research seem to indicate dysfunction in areas implicated in "top-down" cognitive control in the processing of stimuli, which involves prefrontal cortex (PFC), anterior cingulate cortex (ACC) and insula [29 46-48]. Patients with depression, moreover, show a reduced deactivation of the network of neural areas that regulate the resting state (default mode network; DMN), a function that involves cerebral glutamatergic activity [49 50]. The dysfunctional relationship between inefficiency of prefrontal areas that control cognition and altered deactivation of the DMN appears to be more severe in patients with greater degree of rumination [51], suggesting a central role of attention and working memory deficits in depression [52-54].

"Hot" cognition in depression

In the scientific literature, the term "hot" cognition refers to the cognitive functions involved in elaboration of emotionally relevant stimuli [47 55]. The results of the present review on "hot" cognition in depression are summarized in Table II. Executive functions are systematically influenced by emotions in an interaction known as cognitive affective bias (CAB). In depression, studies of CAB have revealed deficits in elaboration of affective stimuli with positive valence and preferential processing of those with negative valence [10 12 26 55 78 91]. This emotional imbalance favouring stimuli with negative valence (referred to as "negative bias") alters many aspects of cognitive functioning in patients with depression, including perception, attention, learning and working memory [55 91 92]. Several authors believe that affective cognitive bias has a central role in the development, maintenance and treatment of depression [10-12 26].

The main neuropsychological studies on CAB in major depression have shown that depressed patients tend to remember negative information better than positive information [56 66 67 71] and to interpret social signs, such as facial expressions, in a more negative (or less positive) manner than healthy subjects [68 70 74 76 93 94]. Moreover, individuals with depression show persistent susceptibility to distractions by emotionally negative stimuli, which acquire an emotional relevance that impairs normal and effective decision-making [95 96]. This type of functioning appears to be in complete contrast with that of healthy subjects, who show an attentive bias towards positive-valenced stimuli [68 72 74 77 81 97]. As a consequence, patients with depression have a decreased ability to divert attention from negative stimuli than healthy subjects [52 53 63 76 88].

Another recently studied domain of "hot" cognition in major depression involves reward and punishment [98]. The significant alteration in the ability to experience gratification, satisfaction and pleasure (anhedonia) is one of the cardinal symptoms for diagnosis of major depression [13]. Studies in this area have reported that depressed patients, compared with healthy subjects, are hypersensitive to failure and to negative outcomes of neuropsychological tests [61 84 99] and, in contrast, relatively insensitive to rewards [80 100 101]. Evidently, the dysregulation of the value reward/punishment attribution to emotional stimuli (or of the positive and negative reinforcement systems) negatively affects the development of learning processes and behavioural strategies that are appropriate to the context [73 79].

At present, there are no well validated techniques for neuropsychological evaluation of the cognitive processes that regulate emotion, and most of the available information on "hot" cognition has been obtained from neuroimaging studies [29 48]. These investigations have demonstrated that the dysfunctions in "hot" cognition involved in the regulation of emotion can be attributed to an abnormal functioning of a network of several cerebral areas [10 29 47 98 102]. One area of research using experimental procedures to assess cognitive performance in depressed subjects (especially memory and attention) in the presence of distracting stimuli (Emotional Go/No-Go task, Emotional Stroop task, etc.), revealed hypofunctioning of the dorso-lateral prefrontal cortex (DLPFC), medial cortex and ACC [95 103 104]. Depressed patients show neurofunctional alterations compared with healthy subjects even in processing of emotionally relevant images. In particular, an increased activation of the amygdala when viewing emotional images with strong negative valence that seems to correlate with the severity of symptoms, has been found in depression [105 106].

Table I. Cold cognition in depression: summary of the main findings.

Study	Test	Results
Alexopoulos et al., 2000 [31]	Mattis Dementia Rating Scale (DRS)	Correlation between performance on initiation/perseveration tasks and relapse/recurrence of depression in subjects aged > 65 years
Majer et al., 2004 [32]	Dual auditory/visual divided attention task of the Test batterie zur Aufmerksamkeitsprüfung (TAP)	Increased risk of relapse in patients with impaired divided attention at discharge
Castaneda et al., 2008 [33]	Trail Making Test A and Digit Symbol-Coding, California Verbal Learning Test-second edition (CVLT-II)	Younger age at depression onset is associated with more impaired executive functioning. Young adults with a lifetime history of depression show mild verbal learning deficits
Herrera-Guzman et al., 2008 [34]	Cambridge Neuropsychological Test Automated Battery (CANTAB)	Depressed patients with good response to bupropion show low pre-treatment levels of mental processing speed and visual memory
McDermott & Ebmeier, 2009 [35]	Meta-analysis	Significant correlations between depression severity and executive function impairment, especially for processing speed and episodic memory alterations
Herrera-Guzman et al., 2010 [23]	Cambridge Neuropsychological Test Automated Battery (CANTAB)	Remitted patients with depression show deficits in planning, sustained attention, working memory, verbal and visual memory. SNRI show higher efficacy in treating verbal and visual memory impairment than SSRI
McLennan & Mathias, 2010 [18]	Meta-analysis	Positive correlation between baseline executive function performance and response to antidepressant treatment
Hasselbalch et al., 2011 [36]	Systematic review	Remitted patients with major depression show impairements of executive function, memory, and sustained/selective attention
Hermens et al., 2011 [37]	Trail-Making Test, part B (TMT B), Rey-Osterrieth Complex Figure Test (ROCF), Rey Auditory Verbal Learning Test (RAVLT)	Poor cognitive flexibility, visual memory, verbal learning and memory in patients with current depressive episode.
Maalouf et al., 2011 [38]	Stockings of Cambridge task (SOC), Rapid Visual Processing task (RVP)	Adolescents with current depression show more impaired executive function and sustained attention compared to adolescents with remitted depression and healthy controls
Lee et al., 2012 [39]	Meta-analysis	Patients with first-episode depression perform significantly worse than healthy controls in cognitive task involving all aspects of executive function (especially attention, psychomotor speed, visual learning and memory)
Wagner et al., 2012 [40]	Meta-analysis	Impaired verbal fluency, cognitive flexibility, and response inhibition in depressed patients compared to healthy controls
Baer et al., 2013 [41]	Montreal Cognitive Assessment (MoCA)	Depressive symptomatology is negatively associated with level of cognitive status one year after retirement
Snyder, 2013 [42]	Meta-analysis	Significantly impaired performance for depressed patients, compared to healthy control, on all neuropsychological measures of executive function. Deficits may be greater in patients with more severe current depression symptoms, and those taking psychotropic medications. Evidence for effects of age was weaker.
Boelen et al., 2014 [43]	Sentence Completion for Events from the Past Test (SCEPT)	Reduced memory specificity is associated with concurrent and later depression in a sample of university students
Li et al., 2014 [44]	Wechsler Adult Intelligence Scale-III, Digit Span subtest (forward and backward), computerized paradigm to test prospective memory	Prospective memory (PM) performance of individuals with high depressive symptomatology (HDS) was significantly poorer than that of low depressive symptomatology participants (LDS). HDS participants were restricted in their allocation of attentional resources to support PM.
Lin et al., 2014 [45]	Rey Auditory Verbal Learning Test (RAVLT)	Higher depressive symptoms scores are associated with lower delayed recall and recognition.

Table II. Hot cognition in depression: summary of the main findings.

Study	Test	Results
Mackinger et al., 2000 [56]	Autobiographical memory task	Women with remitted depression retrieve significantly more categoric descriptions when responding to negative cue words
Mogg et al., 2000 [57]	Attentional faces dot-probe task	Depressed patients show increased attention toward sads faces
Neshat-Doost et al., 2000 [58]	Attentional words dot-probe task	No evidence of attentional bias, either towards depression-related words or threat words in depressed patients
Dozois & Dobson, 2001 [59]	Self-Referent Encoding Task	Depressed patients endorse and recall less positive information compared to anxious and healthy subjects
Murphy et al., 2001 [60]	Computerized decision-making task	Depressed patients show reduced risk adjustment in response to positive reinforcement
Murphy et al., 2003 [61]	Visual discrimination and reversal learning task with negative feedback	Depressed patients show increased tendency to switch responding towards incorrect stimulus following negative reinforcement
Bhagwagar et al., 2004 [62]	Facial expression recognition task	Subjects with a history of depression show a selectively greater recognition of expressions of fear compared to subjects with no history of depression
Gotlib et al., 2004 [63]	Faces dot-probe task	Depressed patients show selective attention to sad faces compared to angry and happy faces
Joormann & Siemer, 2004 [64]	Autobiographical memory and mood regulation task	Reduced ability of positive autobiographical memory to regulate negative mood in depressed patients
Leppanen et al., 2004 [65]	Facial expression recognition task	Depressed patients show reduced speed in recognizing neutral faces and increased tendency to interpret them as either happy or sad
Hayward et al., 2005 [66]	Facial expression recognition and emotional words task	Increased negative bias in the recognition of faces and memory for emotional words after tryptophan depletion
Raes et al., 2005 [67]	Autobiographical Memory Test	Depressed subjects show reduced specificity of autobiographical memory
Joormann & Gotlib, 2007 [68]	Faces dot-probe task	Depressed patients show selective attention to sad faces and absence of positive bias towards happy faces
Joormann et al., 2007 [69]	Autobiographical memory and mood regulation task	Positive autobiographical memory fails to regulate negative mood of depressed patients that, on the contrary, seems to worsen after the recall
Gollan et al., 2008 [70]	Facial expression recognition task	Major depression is associated with reduced speed in the recognition of sad facial expressions and with negative bias towards interpreting neutral facial expressions as sad
Harmer et al., 2009 [71]	Battery of emotional processing tasks	Depressed patients show reduced recognition of positive facial expressions, reduced speed of response to/ memory of positive self-relevant words
LeMoult et al., 2009 [72]	Facial expression recognition following negative mood induction	Patients with recurrent major depression show reduced ability in recognizing happy faces
Chase et al., 2010 [73]	Probabilistic selection task	Depressed patients show a blunting of the training phase of the learning task specifically related to the severity of anhedonia
Milders et al., 2010 [74]	Facial expression recognition task	Patients with major depression show higher accuracy and higher response bias than controls for sad expressions
Anderson et al., 2011 [75]	Facial expression recognition task	Remitted patients show increased emotions recognition due to increased response bias. Currently depressed patients show reduced emotion recognition accuracy
Sterzer et al., 2011 [76]	Variant of binocular rivalry continuous flash suppression	Shorter suppression of sad faces and longer suppression of happy faces in depressed patients compared to healthy controls

(continued)

Table II - follows.

Study	Test	Results
Atchley et al., 2012 [77]	Attentional words and pictures task	Absence of the normal detection bias for positive picture stimuli and person-referent words in depressed subjects
Hu et al., 2012 [78]	Word-face Stroop task	Differently from what happens in healthy controls, depression-related distractor words induce significant emotional conflict to positive target faces in depressed patients
Kunisato et al., 2012 [79]	Probabilistic learning task	Depressed patients show a reward-based decision making deficit and an impaired variability of action selection compared to non-depressed subjects
Treadway et al., 2012 [80]	Effort Expenditure for Rewards Task	Depressed patients are less willing to expend effort for rewards than healthy controls
Everaert et al., 2013 [81]	Spatial cueing task, scrambled sentences test, incidental free recall task	Subclinically depressed patients show negative bias in attention that has an indirect effect on memory via a negative bias in interpretation
Kruijt et al., 2013 [82]	Leiden Index of Depression Sensitivity – Implicit Association Test	Cognitive reactivity and implicit self-depressed associations are significantly associated with depression incidence in a sample of never-depressed individuals
Romero et al., 2013 [83]	Scrambled sentence test, lexical decision task, self-referent incidental recall task	Increased recall of negative self-referent words is predicted by increased negative cognitions at both explicit and automatic level of information processing in remitted depression
Schroder et al., 2013 [84]	Modified Eriksen flanker task	Depressive symptoms are associated to poorer post-error accuracy in difficult reversal blocks in a sample of young adults
Orgeta, 2014 [85]	Facial expression recognition task	Older adults with mild depressive symptoms show reduced ability to recognize facial expressions of fear and anger
Takano et al., 2014 [86]	Think-aloud and time-estimation tasks	Negative thinking is associated with greater judgement errors in females subjects as compared to males with similar levels of depressive symptoms
Vanderlind et al., 2014 [87]	Emotional cuing task	Less cognitive control over negative stimuli predicts increased depression symptoms in a sample of young adults
Yoon et al., 2014 [88]	Working memory task for emotionally-relevant words	Depressed patients show impaired ability to remove irrelevant emotional material from working memory associated with increased rumination
Pfeiffer et al., 2015 [89]	Cognitive reactivity assessment after negative mood induction	Change in depressive thinking in response to negative mood induction is negatively associated with future depression in depressed subjects
Remmers et al., 2015 [90]	Judgment of Semantic Coherence Task	Depressed patients show impaired intuition compared to healthy control participants. Negative affect accounts for the association between rumination and impaired intuition

However, the most widely used functional neuroimaging method to investigate the elaboration of emotional stimuli in depression entails the measurement of the response of patients who are shown emotionally relevant facial expressions [107]. Even these types of studies have consistently reported the presence of an hyperactivation of the amygdala and of an altered connectivity between the amygdala and the ACC in depressed subjects who are shown facial expressions with emotionally negative valence [94 107-109].

As described above, reward processing of emotional stimuli is another system that appears to be altered in depression [98]. Elaboration and processing of stimuli with reward/gratification valence is traditionally studied using techniques that involve winning money or obtaining social gratification [110 111]. These types of methods are designed to evoke the activity of neural areas involved in evaluation of reward, which include the ventral striatum (caudate and putamen), orbital frontal cortex (OFC), mPFC, ACC and its main connections (including the amygdala) [10]. Reduced activation of the caudate and Nucleus Accumbens has been found in

depression before and after receiving an award [112-114]. This phenomenon appears to correlate with the disease status and to be reversible after antidepressant treatment [79 114]. Lastly, as for "cold" cognition, cognitive elaboration of affective stimuli seems to have a role in altered activation of the DMN [115].

Discussion

From 25% to 50% of patients with major depression present with significant compromise in at least one cognitive domain [116]. The most frequently altered cognitive functions during the course of depression are working memory, attention and rate of elaboration of stimuli [9 39]. Such dysfunctions are significantly associated with the frequency of relapse and the duration of disease [117] and are often present before the onset of depression [15] and in the remission phase [35 42 118]. Moreover, cognitive alterations have the greatest impact on patient functioning in major depression [8]. This indicates that cognitive deficits may be considered more as a central element in major depression rather than just secondary phenomena [11].

As previously mentioned, subjects with depression have a decreased ability to distract attention from negative stimuli than healthy individuals [52 53]. This deficit in modulating attention of emotionally relevant information seems to be correlated not only with severity and duration of depressive symptoms, but also with pathological cognitive strategies such as rumination [12 52]. Rumination is a type of recurrent thinking which is self-centred and focused on negative content and which is able to "block" attention on the latter, with a rigid and unproductive use of cognitive resources that interfere with normal cognitive performance and planning of adequate behavioural strategies [52]. Research on the cognitive aspects of depression has indicated that the presence of rumination has important clinical relevance since it can predict episodes of recurrent depression in remitted subjects [52].

Even if for simplicity the mentioned dysfunctional cognitive aspects of depression are divided into "emotionally independent" and "emotionally dependent", there is no reason to consider "hot" cognition and "cold" cognition as two completely separate systems [12 28]. On the contrary, current research on the pathophysiology of major depression is increasingly focused on the interaction between cognition and affective processes, which is referred to as affective cognition [10 26 28]. Studies on affective cognition aim to clarify, for example, how higher order cognitive functions can modulate the elaboration of emotional stimuli (cognitive control) and how processing of emotional stimuli can influence cognitive performance in subjects with depression [28 53 97].

From this point of view, major depression is characterised by an excessive influence of negative emotional stimuli on executive functions ("bottom-up" dysfunction), with a distractive effect on attention, memory and behavioural planning that is at the basis of cognitive deficits [95]. At the same time, the reduced ability of "cold" cognitive systems to inhibit response to negative emotional stimuli ("top-down" dysfunction) is a source of negative interpretation and attribution basis which in turn represents a maintaining factor for depression [119 120].

From a neurofunctional standpoint, such alterations correspond to a dysfunction of cerebral areas involved in the cognitive and emotional elaboration of stimuli [29 48]. In particular, as a confirmation of the coordinated functioning of "hot" and "cold" cognition, an alteration of the reciprocal interaction between the PFC and amygdala has been found in depression during regulation of emotion [121], consisting in a lack of deactivation of the amygdala ("bottom-up" dysfunction) [122-124] and hypofunctioning of the DLPFC ("top-down" dysfunction) [125].

Conflicts of interest: none.

Conclusions

In conclusion, studies on affective cognition have allowed for the development of a single model of reciprocal dysregulation for the cognitive processes in depression [27] that integrates traditional psychological theories about dysfunctional schemes [126] with neuropsychology/neuroimaging data, and involves both "bottom-up" affective bias and "top-down" cognitive bias [28 127]. This view also has important therapeutic implications. In fact, while the efficacy of antidepressants on cognitive symptoms in depression appears to involve normalisation of serotoninergic, noradrenergic and dopaminergic dysregulation at the basis of the "bottom-up" dysfunction of affective cognition (or "hot" cognition), the efficacy of psychotherapeutic strategies with cognitive reinforcement and/or rehabilitation is based on recovery of "top-down" cognitive control of negative emotions (or "cold" cognition) [10 12 26 128 129].

Take home messages for psychiatric care

- Depression is a severe, chronic syndrome with significant impact on functioning and quality of life, and is the leading cause of disability worldwide. Besides its diagnostic value, cognitive impairment associated with depression is relevant as far as vulnerability, course, prognosis, therapy and rehabilitation are concerned
- From 25% to 50% of patients with major depression present with significant compromise in at least one cognitive domain, including working memory, attention and rate of elaboration of stimuli
- Even if for simplicity the dysfunctional cognitive aspects of depression are divided into "emotionally independent" and "emotionally dependent", "hot" cognition and "cold" cognition are not two completely separate systems, but rather depend on the relationship and interaction between cognition and affective processes, which is referred to as affective cognition
- Studies on affective cognition have allowed the development of a single model that integrates traditional psychological theories about dysfunctional schemes with neuropsychology/neuroimaging data, involving both "bottom-up" affective bias and "top-down" cognitive bias
- The efficacy of antidepressants on cognitive symptoms in depression appears to involve the neurotransmitter systems at the basis of "bottom-up" dysfunction of affective cognition (or "hot" cognition), while the efficacy of psychotherapeutic strategies with cognitive reinforcement and/or rehabilitation is based on recovery of "top-down" cognitive control of negative emotions (or "cold" cognition)

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MENTAL HEALTH CARE NEEDS OF INVOLUNTARILY ADMITTED INPATIENTS

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Abstract

Aim: This study examined the association of mental health care unmet needs with involuntary shortest-stay hospitalization in routine psychiatric practice.

Method: 212 adult persons with ICD-10 mental disorders who were consecutively admitted to a 420-bed psychiatric hospital and discharged within 1-7 days were recruited. Participants were evaluated with the Camberwell Assessment of Need Scale (CANSAS-P) at discharge. Patients were grouped voluntary (VA; n=171) or involuntary (IA; n=41) admission.

Results: IA persons with psychotic, neurotic, and personality disorders had a significantly lower mean number of needs (1.4 times less) and unmet needs (1.7 times less) compared to VA persons; they reported lower individual unmet needs including accommodation, food, home, self-care, physical health, treatment, company, basic education, telephone, transport, money, and welfare benefits. Four CANSAS-P domain scores were also found significantly lower in IA than VA inpatients. However, between-group differences for 'social disability' domain scores were unrelated to an effect of age, sex, length of stay, and diagnosis; while 'information processing disability', 'emotional processing disability', and 'coping disability' domain scores were found to be related to diagnoses of inpatients.

Conclusion: These results provide support for the notion that involuntary admission of persons with psychotic, neurotic, and personality disorders is associated with lower or under-estimated perceived mental health care unmet needs compared to voluntary admission.

Key words: Involuntary admission, unmet needs, socio-demographic and clinical features

Introduction

Involuntary hospital admission is specific to psychiatry, assuming that the illness makes it difficult for patients to accept treatment [1 2]. Involuntary psychiatric admission (IA) remains the most restrictive intervention for treatment of mentally disordered patients. IA inpatients have higher suicide rates, lower levels of social functioning, and equal levels of general psychopathology and treatment compliance; they are more likely to be readmitted compulsorily after their index hospitalisation [3-5].

Assessment of mental health care needs is an essential element of psychiatric health care planning and evaluation [6-9]. The most frequently detected needs of persons with psychosis involve psychological distress, house upkeep, food, information on condition and treatment [10-12]. Studies on the needs of acute psychiatric patients are scant [13]. Unmet needs of patients with schizophrenia and schizoaffective disorder strongly correlate with aggressive behavior [14] and quality-of-life outcomes [15]. Personality disorder was found to be independently associated with more unmet needs among psychiatric inpatients [16]. There are, however, no sufficiently

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powered studies that identify unmet needs of involuntary inpatients. Assessment of needs for involuntarily admitted patients is warranted to meet the needs associated with complex and mixed disorders [17].

The present study explored the the following questions:

1 Are there substantial differences in the number of unmet needs between IA and VA groups?
2 What are the between-group differences in frequency of specific unmet needs between IA and VA patients?
3 Are there differences between IA and VA groups in mental health care needs related to demographic and clinical factors?

The authors hypothesized that involuntary admission of persons with mental disorders would be associated with greater unmet health care needs.

Methods

Study design

The data for this study were collected at Sha'ar Menashe Mental Health Center from March 1, 2012 through February 28, 2013. Inclusion criteria: unselected voluntary and civil involuntary admissions in five acute departments; age between 18 and 66 years and duration of hospitalization no more than 7 days (according to the first order of the District Psychiatrist for IA). Involuntary admissions followed national legislation. At the time of the study most of the acute psychiatric patients were admitted to five wards: 4 closed wards (including psychogeriatric department), and one open acute ward. The present study was conducted on the shortest-stay cohort of persons that were admitted during the study period, either voluntarily or under a civil involuntary hospitalization order.

Involuntary hospitalization in Israel

In Israel involuntary psychiatric hospitalization is regulated by the Law for the Treatment of the Mentally Ill, 1991 [18]. The legislative criteria for involuntary commitment in Israel are: (a) acute psychotic state; (b) physical danger to self or others, and (c) a causative link between the psychiatric disorder and the dangerous behavior. The District Psychiatrist is authorized to issue an involuntary hospitalization order (twice for 7 days each time) based on psychiatric examination conducted by a senior psychiatrist. During this period of time, some patients will sign-in as voluntary patients. If the patient does not sign in voluntarily, then he or she is typically discharged after 7-14 days, unless commitment criteria clearly continue to be present. In that case, a District Psychiatric Board (DPB) hearing is scheduled to determine whether or not the legal standard is met for longer-term involuntary hospitalization. The DPB reviews all involuntary commitments, both in the civil and criminal domains. Patients hospitalized under a District Psychiatrist's Order appear before the DPB within 14 days after involuntary hospitalization and every three months thereafter [19]. Since 2004, all patients appearing before a DPB are entitled to receive legal representation. Its purpose is to safeguard the rights of the mentally ill facing compulsory commitment and to help them express their opinion regarding the treatment received and their desire to be discharged from involuntary hospitalization [18 20 21].

During the study period, once admitted, each patient was evaluated by a physician and a treatment team to determine the patient's diagnosis, which was based on the ICD-10 Classification of Mental and Behavioral Disorders [22] When patients were admitted several times, only the first admission was recorded. The following variables were recorded: age, gender, and marital status, education, ICD-10 diagnosis upon admission and at discharge, legal status or the type of admission according to law (voluntary or involuntary), length of present hospitalization (days), number of admissions and duration of hospitalizations for one year before the present admission, reasons for the admission and discharge.

Procedure

The Israeli Law for the Treatment of the Mentally Ill 1991 [18] allows for involuntary commitment under the following circumstances : (a) acute psychotic state; (b) physical danger to self or others, and (c) causative link between psychiatric disorder and dangerous behavior. The District Psychiatrist is authorized to issue an involuntary hospitalization order twice 7 days apart, based on a psychiatric examination. The District Psychiatric Board (DPB) can extend involuntary hospitalization following a hearing held within 14 days of involuntary admission and every three months thereafter [19].

When patients were admitted several times, only the first admission was recorded. The following variables were recorded: age, gender, marital status, education, ICD-10 diagnosis upon admission and at discharge, legal status of admission (voluntary or. involuntary), length of current hospitalization (days), number of admissions and duration of hospitalizations in the year before the current hospitalization, reasons for the admissions and discharges. The Sha'ar Menashe Internal Review Board approved the study.

Sample

Two-hundred-twelve unselected inpatients admitted during one year and discharged after seven (3.9 ± 1.9) days of hospitalization. Among them, 144 (67.9%) men, mean age 36.3 ± 11.3 years (range: 18-66), 215 individuals (58.1%) were single. Mean extent of education was 11.9 ± 3.1 years. Mean age of application for psychiatric care was 26.2 ± 6.5 years, and mean duration of disorder was 21.1 ± 10.2 years. Among 212 patients in the sample 118 (55.7%) presented with ICD-10 schizophrenia spectrum disorders (F20-F29), 25 (11.8%) personality and behavior disorders (F60-F69), 25 (11.8%) with neurotic, stress-related and somatoform disorders (F40-F48), 22 (10.4%) with mood [affective] disorders (F30-F39), 10 (4.7%) with organic mental disorders and intellectual disabilities (F00-F09; F70-F79), and 12 (5.7%) with mental disorders due to psychoactive substance use (F10-F19).

Assessments

Diagnosis was based on a face-to-face interview, medical records, and consensus between two senior psychiatrists. All participants were asked to complete the Camberwell Assessment of Need scale (patient-rated short form; CANSAS-P [8 9 23]. The CANSAS-P assesses needs over the past month for 22 health and social items. The need rating for each item is 0; 'no need' (no problems at all in the domain), 1; 'met need' (no or moderate problems in the domain because of help received), or 2; 'unmet need' (a serious problem, regardless of help provided). Cronbach's a coefficient was 0.85.

The CANSAS-S items appear to fit four CANSAS-P domains. 'Social disability' (5 items): accommodation, food, looking after the home, physical health, information on condition and treatment. 'Information processing disability' (4 items): basic education, telephone, transportation, welfare benefits. 'Emotional processing disability' (6 items): daytime activities, psychotic symptoms, psychological distress, company, intimate relationships, and sexual expression. 'Coping disability' (5 items): self-care, safety to self, safety to others, drugs, child care [23].

Statistical analysis

This report is based on cross-sectional data concerning the legal (voluntary and involuntary) commitment of persons. Univariate comparisons between IA and VA patient groups were evaluated with the c^2 test for equality of proportions for categorical variables and the 2-tailed *t* test, or the Wilcoxon signed rank test (*z*) for assessing continuous variables. The analysis of variance (ANOVA) was applied in order to compare IA and VA patient groups controlling for the following variables: age, sex, length of stay, and diagnosis. Mean values with standard deviation (SD) or standard error (SE) are presented. For all analyses, the level of statistical significance was defined as α less than 0.05. All statistical analyses were performed using the Number Cruncher Statistical Systems [24].

Results

Participants

Among 212 subjects 41 or 19.3% were admitted involuntarily, and 171 or 80.7% subjects were admitted voluntarily : 27 and 117 men among IA and VA, respectively (65.8% *vs* 88.4%, $\chi^2 \pm 0.10$, df ± 1, p ± 0.75). No significant differences between IA and VA were found regarding age (34.2 ± 11.2 *vs* 36.8 ± 11.3, $p > 0.05$), marital status, education, age of onset and illness duration. IA subjects had a slightly longer duration of stay in the current hospitalization (4.7 ± 1.7 days) compared to the VA group (3.8 ± 1.9 days; $p < 0.05$). There were no significant differences between IA and VA in the primary discharge diagnosis (Table I; $\chi^2 \pm 12.4$, df ± 6, p ± 0.054).

Number of needs

The mean number of general needs indicated by patients themselves in the present study was 11.3 ± 6.2 (range 0 to 21); number of unmet needs was 3.8 ± 4.2 (range 0 to 17).

The number of needs identified per VA patients was 1.4 times higher than for IA patients (12.0 ± 5.6 *vs* 8.6 ± 6.4, respectively; t ± 3.2, $p < 0.001$). Figure 1 presents a distribution of involuntarily and voluntarily admitted persons by number of unmet needs. Thirty-one percent of IA persons and tventy-two percent of VA persons did not report their unmet health care needs (24.1% for the entire sample). Between-group differences were significant among inpatients with psychotic, neurotic, personality and behavior disorders (all p's < 0.05; Fig. 2). Furthermore, the number of unmet needs was 1.7 times higher in VA compared to IA persons (4.2 ± 4.3 *vs* 2.5 ± 3.4; $z = 2.5$, p ± 0.011).

Items of needs

For this sample the most frequently detected unmet needs involved psychological distress (40.6%), intimate relationships (34.0%), and sexual expression (25.6%), daytime activities (27.4%), money (25.9%),

Table I. Demographic, background, and clinical features of the sample (n = 212).

Diagnosis at admission (ICD-10)	ICD-10 codes	Involuntary admission (n = 41)		Voluntary admission (n = 171)	
		N	%	N	%
Mental disorders due to psychoactive substance use	F10-F19	3	7.3	9	5.3
Schizophrenia, schizotypal and delusional disorders	F20-F29[1]	11	26.8	73	42.7
Acute and schizoaffective disorder	F23 and F25	11	26.8	23	13.5
Mood [affective] disorders	F30-F39	8	19.5	14	8.2
Neurotic, stress-related and somatoform disorders	F40-F48	2	4.9	23	13.5
Disorders of adult personality and behavior	F60-F69	4	9.8	21	12.3
Organic mental disorders and Intellectual disabilities	F00-F09 and F70-F79	2	4.9	8	4.7

1) Except F23, and F25

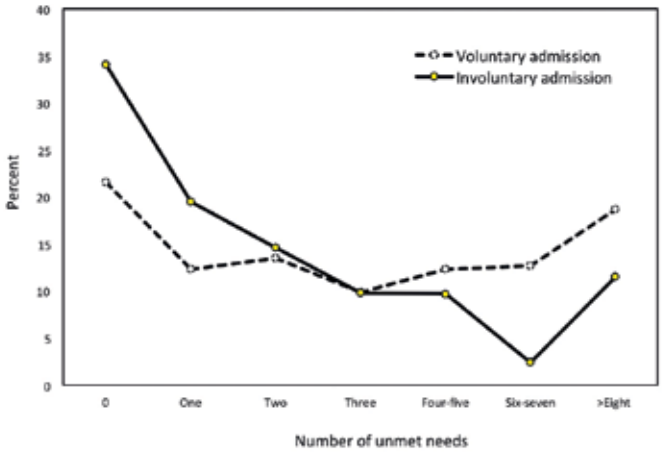

FIGURE 1.
Distribution of involuntary and voluntary admitted persons by numbers of unmet needs.

physical health (25.9%), and company (25.5%) (Table II).

Figure 3 shows significantly decreased frequency of 12 specific unmet needs in IA admitted persons compared to the VA group: accommodation, food, home, self-care, physical health, treatment, company, basic education, telephone, transport, money, and welfare benefits.

Domains of needs

As expected, mean CANSAS-P domain scores were lower in the IA group, than in the VA group, in particular, the social disability (z = 3.4, p < 0.001), information processing disability (p = 0.002), emotional

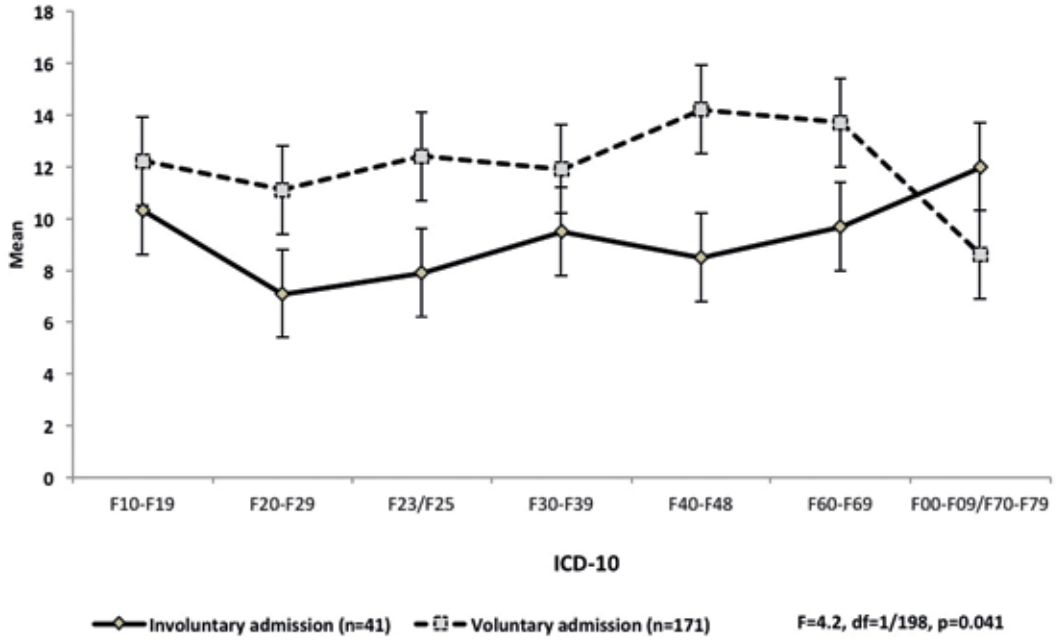

FIGURE 2.
Mean number needs by diagnosis, legal involuntary and voluntary admission.

Table II. Frequency of the CANSAS items in the sample of 212 admitted persons.

Variables	No need		Met need		Unmet need	
	n	%	n	%	n	%
Accommodation	83	39.2	96	45.3	33	15.6
Food	99	46.7	102	48.1	11	5.2
Looking after the home	84	39.6	93	43.9	35	16.5
Self-Care	82	38.7	106	50.0	24	11.3
Daytime activities	66	31.1	88	41.5	**58**	**27.4**
Physical Health	70	33.0	87	41.0	**55**	**25.9**
Psychotic symptoms	108	50.9	63	29.7	41	19.3
Information on condition and treatment	74	34.9	121	57.1	17	8.0
Psychological distress	54	25.5	72	34.0	**86**	**40.6**
Safety to self	117	55.2	47	22.2	48	22.6
Safety to others	173	81.6	30	14.2	9	4.2
Alcohol	159	75.0	22	10.4	31	14.6
Drugs	169	79.7	21	9.9	22	10.4
Company	66	31.1	92	43.4	**54**	**25.5**
Intimate relationships	89	42.0	51	24.1	**72**	**34.0**
Sexual Expression	100	47.4	57	27.0	**54**	**25.6**
Child Care	145	68.4	48	22.6	19	9.0
Basic Education	101	47.6	87	41.0	24	11.3
Telephone	110	51.9	96	45.3	6	2.8
Transport	108	50.9	83	39.2	21	9.9
Money	70	33.0	87	41.0	**55**	**25.9**
Benefits	88	41.5	82	38.7	42	19.8

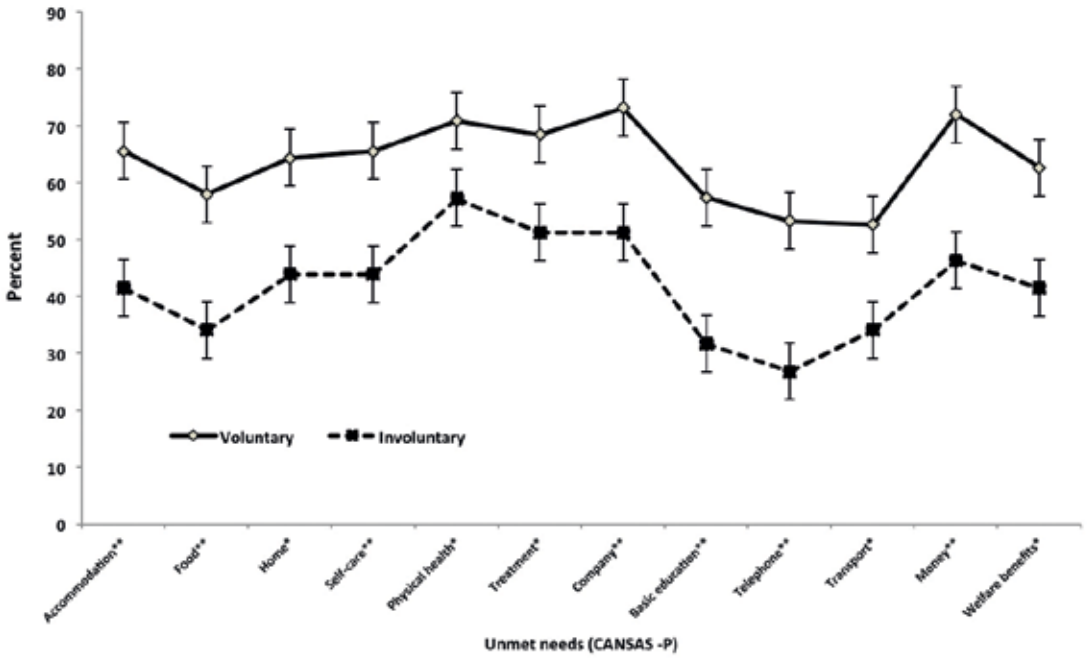

FIGURE 3.
Frequency of the specific unmet needs: voluntary *vs* involuntary admission.

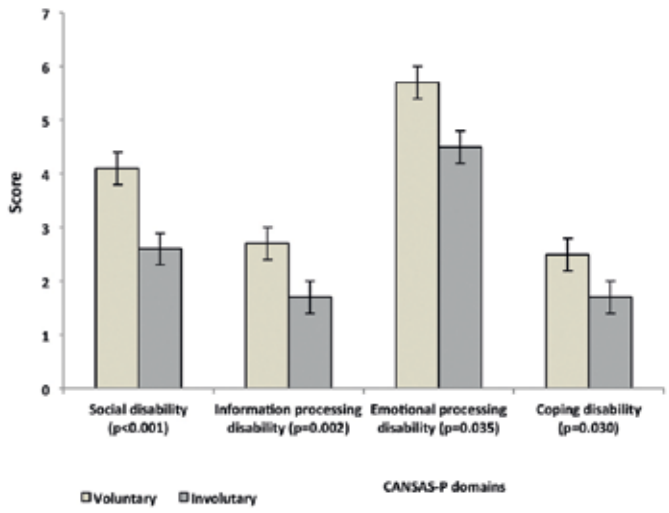

FIGURE 4.
Mean CANSAS-P domain scores: voluntary *vs* involuntary admission.

processing disability (t ± 2.1, p = 0.035), and coping disability (z = 2.2, p = 0.030) (Fig. 4).
When IA and VA patient groups were compared with ANOVA controlling for age, sex, and length of stay, between-group differences in the mean number of needs, and all CANSAS-P domain scores remained significant (all p' < 0.05). Controlling for the ICD-10 diagnosis (as a second factor) ANOVA showed loss of between-group differences for information processing disability (p = 0.071), emotional processing disability (p = 0.085), and coping disability (p = 0.064), but not for social disability (p = 0.027), or the mean number of needs (p = 0.041).

Discussion

The assumption was that involuntary admission would be associated with greater unmet health care needs.
The first research question addressed differences between IA and VA inpatients in the number and and frequency of specific unmet needs. This study revealed that the mean number of unmet needs was 3.8 ± 4.2 that replicated data from previous publications [10 12 25 26]. Patients followed by community-based mental health services revealed a similar number of clinical and social needs, while inpatients (with the exception of acute patients) revealed more social needs [27]. Rates of the mean number of needs (1.4 times less) and unmet needs (1.7 times less) were significantly lower among IA persons with psychotic, neurotic, and personality disorders compared to a matched VA sample.
The second research question addressed differences in frequency of specific individual unmet needs between IA and VA groups. Descriptive findings suggest that the the highest proportion (25% to 40%) of unmet needs were psychological distress, intimate relationships, and sexual expression, daytime activities, money, physical health, and company, that is consistent with previous studies [12 15 16 28]. IA persons reported lower unmet needs regarding accommodations, food, home, self-care, physical health, treatment, company, basic education, telephone, transport, money, and welfare benefits compared to VA persons.
The third research question addressed the effects of demographic and clinical factors on differences between IA and VA groups in the domains of mental health care needs. ANOVA was performed with the following covariate variables (age, sex, length of stay, and diagnosis). Although scores of domain needs were significantly lower in IA than in VA inpatients, between-group differences for 'information processing disability', 'emotional processing disability', and 'coping disability' domain scores were associated with diagnoses of inpatients, while 'social disability' domain scores were unrelated to demographic and clinical covariates.
Contrary to our expectations, involuntary admission was associated with lower unmet health care needs than VA subjects. The most plausible explanation might be related to the fact that IA patients do not have unmet needs in many of the areas of medical care; or that they were under-estimated by IA persons. Both of these assumptions are tenable.
One explanation for this finding might be self-report methodology for investigating mental health needs in psychiatric inpatients. A perceived unmet need is not equivalent to an objectively assessed unmet need. Perceived unmet need for treatment strongly correlated with level of distress and impairment in role functioning. Similar correlations have been found in prior research [29]. Significant differences in the perceptions of voluntarily re-admitted inpatients who met ICD-10 criteria for schizophrenia and schizoaffective disorders and staff occurred in 6 of the 22 needs, with patients rating the needs for "information on condition and treatment" and "benefits," higher, and the staff member rating the patients' needs for "intimate relationships"; "safety for others," "self-care" and "daytime activities", higher. Analogical differences occurred between the patients and their relatives in the same need areas [30].
An additional explanation for this finding might be re-

lated to lack of insight. A majority of persons suffering from mental illness show limited insight into their illness, their symptoms as part of an illness, treatment and health care needs. Involuntarily committed patients were significantly less likely than voluntarily admitted patients to acknowledge that they were psychiatrically ill and in need of treatment [3 31] and that could result in worrying about relationships, living situation, health and finances [32].

Multiple studies have shown correlations between poor medication adherence and lack of insight across diagnostic groupings [33-34]. Former IA patients continue to be more sensitive to subjective or real coercion in their treatment and more vulnerable to medication non-adherence; they felt coerced more frequently in several treatment aspects at follow-up assessments [35].

Limitations: This study deals with a 'truncated' sample, the shortest-stay cohort of persons that was discharged after 7 days in hospital. Second, the sample size of IA group of inpatients was relatively small. Third, use of self-report methodology for investigating mental health needs in severely ill psychiatric patients. However, this is the first report on differences in perceived mental health care needs between IA and VA persons. Given that unmet needs may be under-estimated, it can be concluded that unmet needs are important targets for the treatment of IA patients.

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AN UPDATE OF THE PRECLINICAL PROFILE OF LURASIDONE

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Abstract

Lurasidone is a novel antipsychotic drug approved by the US Food and Drug Adminstration (FDA) for the treatment of schizophrenia and bipolar disorder in adults, and by the European Medicines Agency (EMA) for the treatment of schizophrenia.

This article reviews published preclinical studies, and analyses the pharmacological, behavioural and molecular mechanisms of lurasidone and their contribution to its therapeutic activity.

Lurasidone is an antagonist for dopamine D_2, serotonin 5-HT_{2A}, and 5-HT_7 receptors, and a partial agonist for serotonin 5-HT_{1A} receptors, whereas it has negligible affinity for histamine H_1 and muscarinic M_1 receptors.

Studies with animal models predictive of antipsychotic and antidepressant activities demonstrated a high efficacy of lurasidone. Moreover, pro-cognitive effects were observed in several animal models that assessed memory, cognition and executive functions. The clinical meaning of these results in human patients is not well understood, yet.

At a cellular level, lurasidone promoted neuronal plasticity, modulated epigenetic mechanisms controlling gene transcription, and increased the expression of the neurotrophic factor BDNF in cortical and limbic brain regions.

Key words: Lurasidone, schizophrenia, bipolar disorder

Introduction

Second-generation antipsychotics have been widely used for schizophrenia. Drugs, such as olanzapine, ziprasidone, risperidone, clozapine, and quetiapine, share the ability to antagonize D_2 and 5-hydroxytryptamine$_{2A}$ (5-HT_{2A}) receptors. They are effective for treating positive symptoms, such as hallucinations, delusions, and excitement, and may improve negative symptoms (flattened affect, apathy, and social withdrawal) [1,2]. Unfortunately, many second-generation antipsychotics (e.g., clozapine and olanzapine) are associated with a high risk of metabolic dysfunction and weight gain [3]. This drawback of available drugs caused an unmet medical need for new agents for the treatment of schizophrenia, with a good safety profile.

Lurasidone [(3aR,4S,7R,7aS)-2-{(1R,2R)-2-[4-(1,2-benzisothiazol-3-yl) piperazin-1-ylmethyl]-cyclohexylmethyl}-hexahydro-4,7-methano-2H-isoindole-1,3-dione hydrochloride] is a novel azapirone derivative, an antipsychotic drug approved by the US Food and Drug Adminstration (FDA) for the treatment of schizophrenia and bipolar disorder in adults, and by the European Medicines Agency (EMA) for schizophrenia patients [4,5]. Preclinical studies demonstrated that lurasidone has antipsychotic, anxiolytic and antidepressant effects in rodents; such efficacy

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was associated with a low potential to induce extrapyramidal side effects [6]. Lurasidone proved to be effective in the treatment of acute schizophrenia, acting both on positive and on negative symptoms, and to be well tolerated [7]. Receptor binding affinities, structural features and neuroplastic properties (shown in animal models) may contribute to the pharmacological profile of lurasidone, which could explain the clinical efficacy.

Lurasidone has high affinity as antagonist for dopamine D_2, serotonin 5-HT_{2A}, and 5-HT_7 receptors, and as partial agonist for serotonin 5-HT_{1A} receptors, whereas it has and negligible affinity for histamine H_1 and muscarinic M_1 receptors, which are thought to contribute to side effects such as weight gain, sedation, and deterioration of cognitive function [4].

Studies with animal models predictive of antipsychotic and antidepressant activities demonstrated a potential high efficacy of lurasidone. Moreover, this novel drug had pro-cognitive effects, as shown in several animal models that assessed memory, cognition and executive functions. At a cellular level, lurasidone promoted neuronal plasticity, modulated epigenetic mechanisms controlling gene transcription, and increased the expression of the neurotrophic factor BDNF in cortical and limbic brain regions [4].

This review focuses on the preclinical evidence on lurasidone. Data on the pharmacological profile, receptor binding activity, behavioural and molecular mechanisms are reported highlighting their potential contribution to the therapeutic characteristics of the drug. Information is based on published preclinical studies, and product labels.

Methods

This article is based on published preclinical studies, accessed by querying the literature databases PubMed and EMBASE, for the search term “lurasidone” and reviewing articles with preclinical information. Product labeling provided further information, and the manufaturer’s website was examined.

Pharmacology

Pharmacokinetics

Lurasidone is rapidly absorbed after oral administration, reaching the peak plasma concentration in 1-3 hours [5]. The adsorption is highly increased when the drug is administered with food; the area under the curve and C_{max} are increased 2- and 3-fold respectively in fed versus fasting subjects. Area under the curve and C_{max} increase linearly with the dose between 20 and 160 mg. Steady state is reached in 7 days [5]. Protein binding is extensive (99.8%), with a high affinity for albumin and α-1-glycoprotein. Lurasidone is a substrate for CYP3A4 [8], and has two active metabolites ID-14283 and ID-14326, representing approximately 25% and 3% of the exposure to the parent compound. Hepatic metabolism of lurasidone contributes to its low bioavailabilty, that may explain the effect of food on lurasidone adsorption [9]. Renal and hepatic impairment can increase the exposure to lurasidone [5]. The mean elimination half life of lurasidone is 18 hours, but may be longer after the steady state has been reached [8]. This half life falls in the range that is considered safe for administration once a day with reasonable efficacy and tolerability [9].

Pharmacodynamics

Receptor binding affinities were determined in experiments with cloned human receptors or animal tissue membrane fractions. High affinity was shown for 5-HT_7 (K_i = 0.5 nM), D_2 (K_i = 1.6 nM), 5-HT_{2A} (K_i = 2.0 nM), 5-HT_{1A} (K_i = 6.8 nM), and adrenergic α_{2C} (K_i = 10.8 nM) receptors. Lurasidone had moderate affinity for α_1 (K_i = 48 nM) and α_{2A} (K_i = 41 nM) receptors, weak affinity for D_1 (K_i = 262 nM) and 5-HT_{2C} (K_i = 415 nM), and very low affinity for histamine H_1, muscarinic, nicotinic, glutamate and sigma receptors, and dopamine and serotonin transporters (see Table 1)[6].

Lurasidone is an antagonist of D_2 and 5-HT_7 receptors and a partial agonist of 5-HT_{1A} receptors [6]. In vitro studies showed that it antagonizes [^{35}S]GTPγS binding stimulated by dopamine in D_2 membrane preparations and antagonizes 5-HT-stimulated cAMP accumulation in CHO/h5-HT_7 cells. Binding of [^{35}S]GTPγS to human 5-HT_{1A} membrane preparations was partially stimulated [6]. In vivo studies with microdialysis found that lurasidone dose-dependently and preferentially increased ratio of dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC)/dopamine in frontal cortex vs striatum of adult rats [6].

Receptor occupancy was studied in vivo to evaluate the contribution of receptor subtypes to the antipsychotic activity of lurasidone and to provide evidence for the low liability to induce extrapyramidal side effects. Dopamine and serotonin are considered pivotal neurotransmitters in schizophrenia and their receptors represent an important target for the action of antipsychotic drugs. Antagonism of D_2 receptors in the mesolimbic system is important for the treatment of positive symptoms in schizophrenia, while block-

Table I. Receptor binding affinity of lurasidone as compared to three major second-generation antipsychotic drugs: risperidone, olanzapine, and clozapine [6].
Lurasidone demonstrated greater receptor binding affinity (lower Ki values) for 5-HT_7 receptors than other atypical antipsychotics tested, as well as high D_2 and 5-HT_{2A} binding. Lurasidone also exhibited relatively high receptor binding affinities for 5-HT_{1A}, and α_{2C} receptors, but negligible binding at H_1 and M_1 receptors.

Receptor Subtype	Ki (nM)			
	Lurasidone	Risperidone	Olanzapine	Clozapine
Serotonergic 5-HT_7	0.5	2.7	–	42.2
Dopaminergic D_2	1.7	2.9	14.4	108
Serotonergic 5-HT_{2A}	2.0	0.2	5.8	9.2
Serotonergic 5-HT_{1A}	6.8	262	> 1000	123
Adrenergic α_{2C}	11	11	–	16
Adrenergic α_{2A}	41	13.7	–	147
Adrenergic α_1	48	1.4	22	17.5
Histamine H_1	> 1000	3.5	3.8	2.0
Muscarinic M_1	> 1000	> 1000	7.6	4.9

ade of D_2 receptors in other brain structures may cause side effects [10].
One important aspect in the pharmacodynamic profile of lurasidone is represented by its affinity, as antagonist, at serotonin 5-HT_7 receptors, which has drawn great interest for central nervous system disorders also considering that different antipsychotic and antidepressant drugs have affinity for this receptor subtype [11]. 5-HT_7 antagonism has been associated with antidepressant properties and pro-cognitive effects in several animal models, suggesting that it can be relevant to ameliorate mood and cognitive impairments in individuals suffering from psychiatric disorders [4,6]. Using [^{3}H]SB-269970 autoradiography, it was demonstrated that 5-HT_7 receptors are expressed in rat limbic brain structures. Lurasidone showed concentration-dependent inhibition of the radioligand binding in various regions of the rat brain [11].
Considering that dose-dependent changes in receptor occupancy may differentially impact gene transcription, acute and chronic treatments with different doses of lurasidone (1, 3 and 10 mg/kg) were used to investigate its ability to modulate the expression of the activity-regulated genes Arc, Zif268 and Npas4, which are markers of neuronal activation and are also associated with neuroadaptive mechanisms. Dose-dependent and anatomically-selective differences after acute and chronic lurasidone treatment were observed. Acute treatment with different doses of lurasidone appears to exert modulatory activity in different brain regions based on selected neurotransmitter receptors. In fact, low doses of the drug were effective in the hippocampus, while high doses were active in the striatum, reflecting the high predominance of D_2 receptor expression in this brain region. On the contrary, chronic treatment with lurasidone revealed a different pattern of gene modulation, suggesting that repeated drug exposure may lead to neuroadaptive changes affecting specific brain regions in a dose-dependent manner [12].

Activity in behavioural models of disease

Behavioural studies found that lurasidone is effective in several animal models of psychiatric disease [4].

Antipsychotic activity

Lurasidone at doses 1-10 mg/kg dose-dependently inhibited conditioned avoidance response in rats behaviour when administered 1 hour before the test, with a median ED_{50} of 6.3 mg/kg [6 13].
Administration of lurasidone before the injection of methamphetamine dose-dependently inhibited the locomotor hyperactivity in adult rats for > 8 hours, providing evidence of D_2 receptor blockade [6].

Activity on cognitive impairment

Lurasidone in a dose range between 1 and 30 mg/kg

did not affect learning and memory functions in rodents, as assessed by the passive avoidance test. In addition, it reversed the impairment of the response induced by MK-801, suggesting that lurasidone can restore the memory consolidation process disrupted by MK-801. This mechanism may be clinically useful for the treatment of cognitive deficits of schizophrenia [14]. In addition it was suggested that the 5-HT_7 receptor antagonistic activity of lurasidone has a role in this process of ameliorating MK-801-induced cognitive deficits in the rat passive avoidance test [15].
Lurasidone at doses between 1 and 3 mg/kg significantly decreased the escape latency, swimming distance, and frequency of diving behaviours in rats treated with MK-801 at a dose of 0.15 mg/kg [16].
Eventually, it reversed the impairment of novel object recognition (considered a measure of working memory) induced by phencyclidine. This effect was dependent on lurasidone activity as partial agonist at 5-HT_{1A} receptors and as an antagonist at 5-HT_7 receptors [17 18].

Activity on models of depression
Lurasidone reduced the immobility of mice in the forced swim test at doses between 0.3 and 1.0 mg/kg, showing an antidepressant effect. Lower doses of lurasidone alone were not effective but combined with a low dose of citalopram reduced immobility [19]. It was also observed that this effect was not present in mice lacking functional 5-HT_7 receptor, suggesting that the interaction with this serotonergic receptor subtype may mediate the antidepressant activity of lurasidone [19].

Neuroplastic properties. Second generation antipsychotics are widely used for the treatment of disorders characterized by impaired emotional control. Clinical improvement relies on the complex and heterogeneous receptor profile of these drugs but it is also highly dependent upon neuroadaptive and neuroplastic changes that take place following prolonged drug exposure. Along this line of reasoning, we have demonstrated that chronic administration of lurasidone in rats increased the expression of brain-derived neurotrophic factor (BDNF) in hippocampus and prefrontal cortex under basal conditions, and it is also able to modulate neurotrophin responsiveness to stress, which represents a major precipitating element in psychiatric disorders [20]. The modulation of mechanisms correlated with neuronal plasticity may contribute to the amelioration of cognition that is deteriorated in schizophrenic patients.

More recently, the ability of chronic administration of lurasidone to improve emotional control was further investigated in serotonin transporter (SERT) knockout rats, an animal model of mood disturbance. Genetic deletion of SERT in rodents leads to fear extinction, anxiety and depression. This model also exhibits alterations of neuronal plasticity, with a reduced expression of BDNF in the hippocampus and prefrontal cortex [21]. Behavioural experiments showed that lurasidone increased fear extinction in SERT knockout rats, but not in wild type control animals [21]. As BDNF in the prefrontal cortex is known to have a relevant role in fear extinction, we also investigated whether the expression of the neurotrophin could be modulated by lurasidone administration to SERT knockout rats. It was found that lurasidone modulated the levels of specific transcripts in the prefrontal cortex, leading to a normalization of neurotrophin defects associated with SERT deletion [21].
Lurasidone was also investigated in a model of prenatal stress, a condition relevant for mood disturbance. Indeed, on the basis of epidemiological and experimental evidence, it is known that environmental challenges during pregnancy may increase the risk for psychopatology in adulthood [22]. Accordingly, it was also found that exposure to early adversities and stress produced a significant reduction of neuronal plasticity. As an example, we have shown that exposure to prenatal stress leads to a significant reduction of BDNF expression in prefrontal cortex [23 24], which may contribute to the behavioral phenotype of rats born from females stressed during late gestation, including decreased ability to cope with stress, anxious behaviour and depressive-like disturbance. Treatment with lurasidone during adolescence was able to prevent the reduction of BDNF expression in adult rats that had been exposed to prenatal stress [22].
Recently, it was investigated if combination of lurasidone with a mood stabilizer could determine increased changes in neuronal plasticity, in the hypothesis that combinatory strategies rely not only on receptor and synaptic mechanisms but also on long-term downstream targets, that seem to be relevant for functional recovery [25]. Co-administration of lurasidone and valproate produced, when compared to the single drugs, a larger increase in the expression of specific neurotrophin transcripts in the ventral hippocampus. Lurasidone alone up-regulated the mRNA levels of both total and long 3' UTR BDNF (total: +43%, $p < 0.001$ *vs* vehicle; long 3' UTR: +46%, $p < 0.001$ *vs* vehicle); valproate increased only the long 3' UTR BDNF mRNA levels (+26 %, $p < 0.05$ *vs*

vehicle). The combination of the two drugs produced a more robust increase of the long 3' UTR BDNF transcript when compared to the single drugs (+74%, $p < 0.001$ *vs* vehicle; +18 %, $p < 0.05$ *vs* lurasidone; +38%, $p < 0.001$ *vs* valproate-treated animals) [25].
Interestingly the modulatory activity of lurasidone-valproate combination is specific for the ventral hippocampus that is primarily involved in the modulation of emotional response and affective states, through its connections with the cortex and the amygdala.

Discussion and Conclusions

Lurasidone was approved by the FDA for the treatment of schizophrenia and bipolar disorder and by EMA for schizophrenia patients, after its activity and safety was established in clinical studies. It has a benign metabolic profile and a low incidence of serious adverse events. Lurasidone has the highest affinity for serotonin 5-HT_7 receptors that may play an important role for cognition and mood, followed by dopamine D_2 receptor and serotonin 5-HT_{2A} and 5-HT_{1A}, with negligible affinity for muscarinic M_1 or histamine H_1 receptors [6]. This receptor binding profile is predictive of activity on psychotic symptoms, with a low potential for extrapyramidal and metabolic side effects. Behavioural tests showed that lurasidone was effective in different animal models of disease, predictive of antipsychotic, and possibly pro-cognitive and antidepressant efficacy. On this basis, lurasidone should present good efficacy for the treatment of patients. If lurasidone displays the capacity to improve cognitive deficits, which represent a major unresolved issue for psychiatric patients [4], is a question that needs to be answered through clinical trials, properly designed to assess cognitive function in this patient population.
Molecular and cellular studies demonstrated that lurasidone is very effective in increasing the expression of the neurotrophin BDNF in the prefrontal cortex of rats after long-term administration. The ability of lurasidone to enhance neuroplasticity that is impaired in schizophrenia and mood disorders may represent an add-on value for long-term efficacy in clinical use [4].
In conclusion, the available preclinical data support the efficacy of lurasidone on psychotic symptoms, with both short-term and long-term effects, with a potential for amelioration of depressive component and of functional capacities that are deteriorated in patients with schizophrenia, bipolar disease and depression.

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Take home messages for psychiatric care

- Lurasidone is a novel second generation antipsychotic (SGA) approved by the US Food and Drug Adminstration (FDA) for the treatment of adult patients with schizophrenia or bipolar depression and by the European Medicines Agency (EMA) for patients with schizophrenia
- Available preclinical data provide a characterization of the pharmacological profile suggesting a high potential for clinical efficacy associated with good tolerability. While, similar to other SGAs, lurasidone is an antagonist at D_2 and 5-HT_{2A} receptors, it is also a potent antagonist at 5-HT_7 receptors, a feature that may hold implications for its activity on cognitive deficits that are present in psychiatric patients
- The potential clinical implications of the 5-HT_7 receptor antagonism need to be further studied in this patient population

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REMISSION IN DEPRESSION AFTER TREATMENT: TOO OBVIOUS TO CLINICIANS, WHY SO DIFFICULT TO MEASURE?

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Abstract
The standard of reference for the prognosis of depression has substantially changed from "response" to "remission", since this last is associated with better indices of the course of illness. The treating psychiatrist must now reconsider his approach and refer to remission as the ultimate goal of treatment. Otherwise, patients with incomplete remission could even blame the treating psychiatrist for their enduring illness. The use of simple, short psychometric scales, like the CGI-S, could facilitate this approach, since scores of "1" and "2" are reasonable proxy for remission, as shown by recent literature.

Key words: depression, remission, Hamilton Depression Scale, Clinical Global Impression

The border between a successful treatment and a failed treatment in medicine is based on whether pre-established goals are reached. These standards are accepted by the international scientific community and are susceptible to variation over time as knowledge progresses.
In general, when evaluating the effectiveness of a given treatment, medical doctors rely on objective and quantitative measures, such as blood pressure, electrocardiograms, blood chemistry and imaging techniques; these measures are directly related to the pathophysiology of a given disorder.
Psychiatry is most probably a major exception to this approach, because in this discipline the outcome evaluation is still based on purely descriptive information, taken from a direct visit with the patient. This evaluation has a broad range of subjective interpretations and is in no way connected to the pathophysiology of the disorder.
In this general framework, different labels have been used to evaluate the efficacy of antidepressant treatments after the introduction of tricyclics and the mono-ammine oxidase inhibitors: "improvement", "response", "clinical remission" or, more rarely "functional remission" and "recovery".
Some of these indicators, for example, "functional remission" and "recovery", are more a wishful goal than really true measures to evaluate a successful treatment. To satisfy these definitions, other factors are needed that are independent from drug treatment. The factors that could favour or hamper a full "functional remission" and/or "recovery" should definitely include the attitude of persons in close contact with the patient toward depression, difficulties in starting a new job under actual economic conditions, and, more generally speaking, the presence of barriers due to the stigma related to mental illness in general and its treatment.

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From a broader perspective, one must realize that the different criteria to evaluate a successful antidepressant treatment have substantially different meanings. For example, "improvement" and "response" imply a reference to a previous evaluation, whereas "clinical remission", "functional remission" and "recovery" are in some ways an almost absolute state, unrelated to any previous phase of a patient's history. Furthermore, "response", "clinical remission", "functional remission" and "recovery" refer to definite cut-offs on psychometric scales, whereas "improvement" does not imply pre-defined quantitative criteria, for it simply describes the pure judgement that the clinical picture is somehow better compared with a previous evaluation and does not commit to any estimate of the rate of improvement. Finally, "improvement", "clinical remission", "functional remission" and "recovery" also still maintain their value and meaning when no specific treatment is started, whereas the label "response" should more properly satisfy the assumption of a definite cause–effect link between treatment and amelioration of the clinical condition.

All these differences are not purely semantic. On the contrary, they have a substantial effect on the prognosis of a patient with depression. It is notable that the indicators of a successful treatment have changed from "improvement" and "response" to the more recent and more rigorous "clinical remission".

Compared with patients showing improvement or a general response to treatment, those who reach "clinical remission" have many better prognostic indicators. A huge amount of data from the recent literature clearly state that, compared with those who are responders only, patients with "clinical remission" have a lower number of relapses and recurrences, have a longer euthymic period, a lower risk of a chronic course, as well as a better working and social functioning, less days off work, a less frequent unemployment status, and a lower use of general medical services [1-14].

These data strongly sustain the unanimous position of the scientific community that has established "clinical remission" as the gold standard for a successful treatment, which means reaching an almost or even completely asymptomatic state. However, this largely held conviction is not echoed by a unique choice of criteria and evaluation scales to designate the state of "clinical remission". Indeed, time after time, different rating scales have been used, particularly the Hamilton Rating Scale for Depression, the Montgomery-Äsberg Depression Rating Scale and the Quick Inventory for Depressive Symptomatology, and even different versions of the same scale, different cut-off scores, and different time lengths for "clinical remission" [8,11,13]. Not surprisingly, these differences are sometimes associated with differences in results [13].

Despite this variability in criteria, the standard of "clinical remission" has been widely accepted in clinical studies on the effectiveness of different antidepressant treatments, both pharmacologic and nonpharmacologic. This is proved by the fact that, since the new millennium, almost all trials on the treatment of depression published in international journals have included a state of "clinical remission" among the different indicators of a successful treatment.

In the routine clinical treatment of depression, acceptance of the concept of "clinical remission" as a necessary reference to define a successful treatment is far less rooted. Some doctors, psychiatrists or not, aim to reach a "clinical remission" state in their treatment efforts, but many others, the majority throughout the world, still pursue a vague "improvement" or a good "response" as the ultimate treatment goal for their patients. The choice of not updating one's decisional algorithm about depression treatment according to proper assessment standards means that a treatment project cannot be correctly implemented; if a clinician is satisfied with the "improvement" or "response" of his patient without having reached "clinical remission", he or she will be supporting the continuation of drugs that are only partially effective, and avoiding a change in drug posology or treatment until "clinical remission" is reached. For the patient, this means possibly damaging care over time, not deserved, that could lead to a legal case for malpractice. For these reasons, it is mandatory that the doctor treats a patient with depression with the settled goal of "clinical remission".

The need to identify a definite anchor point to state if a patient with depression is in "clinical remission" is generally accepted in the research field, but in clinical practice it cannot be transferred easily, because the use of psychometric scales and structured interviews is still largely an exception. The reasons why clinicians are not used to considering psychometric tools as the basis for a proper evaluation are manifold.

Among these are the lack of training in using rating scales, not being acquainted with the basic principles of the reliability and validity of a scale, considering the products of scientific reports as academic affairs that are not to be fully and quickly transferred to clinical practice, the inadequacy of training networks, and, most of all, the work burden that is supposedly

limiting the time available to properly administer the rating scales.

The lack of available time may be only a partial justification. Indeed, it is true that 15-20 minutes are needed to complete the Hamilton Rating Scale for Depression and the Montgomery-Äsberg Depression Scale, but it is also true that the Quick Inventory of Depressive Symptomatology needs only 5-10 minutes and this does not truly vary the length of time required for the clinical evaluation of a depressed patient.

Furthermore, the Quick Inventory of Depressive Symptomatology is often used effectively in its self-administered form, so that it does not interfere with the timetable of the physician. Psychiatrists who are very refractory to the use of rating scales to diagnose clinical remission of depression should use at least the Clinical Global Impression-Severity Scale. There are two main reasons for recommending it. First, this scale bypasses the issue of time available on the part of the clinician because it quickly rates the severity of depression, as this unravels during the routine clinical evaluation. To rate the scale requires only 1-2 minutes. Second, since the Clinical Global Impression scores correlate well with the Hamilton Rating Scale for Depression and the Montgomery-Äsberg Depression Scale [15], one can assume that a score of "1" and possibly "2" stands for "clinical remission".

Actually, in a recently published study [13] on remission in 907 outpatients treated with antidepressant medications by 41 community psychiatric centres in Italy, the VIVAL-D study, we found that the correlation between Clinical Global Impression-Severity Scale scores and the HAM-D17 was very high, with a Spearman correlation coefficient of 0.63, and, taking the usual HAM-D17 cut-off of 7/8, patients with a CGI rating of "1" and "2" were in clinical remission in 92.3% and 57.3% of cases, respectively. Our results further underline how clinicians can make a reliable and valid rating of remission through the use of quick and easy psychometric scales.

We also found that only a minority of patients reached a complete symptom-free condition. This in turn should alert clinicians to the possibility that a few symptoms may hinder functional remission. It is reported [16] that cognitive disturbances are among the most common residual symptoms of depression in spite of treatment, and probably newer pharmacological approaches to cognitive dysfunction will be needed that will cooperate with other interventions.

Recent findings have revealed that antidepressant drugs reactivate a window of plasticity in the adult cortex [17] and that functional remission from depression is a gradual process that unfolds slowly, facilitated by structured guidance and rehabilitation. The evaluation of psychosocial functioning and health related quality of life has been poorly investigated by recent research [18], but the CGI, while asking a clinician to compare a subject to typical patients in the clinical experience, encompasses some evaluation of the overall performance too.

Finally, although every effort should be pursued by the psychiatrist in treating aggressively depression, a clinician must remember that some variables may hinder remission, like temperament [18] and epigenetic effects during early development [17].

However, if the knowledge about remission would inform the clinical approach to a depressed patient, the quality of treatment will ultimately improve, with significant impact on a patient wellbeing and overall performance.

Take home messages for psychiatric care

The standard of reference for the prognosis of depression has now changed from "response" to "remission"
Data from the literature evidence many better prognostic indicators associated with remission
Improvement or response should no longer be the ultimate goal of treatment
Not treating a patient until remission could possibly lead to a legal case for malpractice
The use of psychometric scales in clinical practice is still largely an exception
The Clinical Global Impression – Severity Scale requires only 1-2 minutes to be rated
Data from a recent, large epidemiological survey in 41 psychiatric centers of Italy have shown that ratings of "1" and "2" of the CGI were valid proxy for clinical remission

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