

## Bipolar disorder treatment guidelines and their limits in every day clinical practice

*Linee guida per il trattamento del disturbo bipolare e loro limiti nella pratica clinica quotidiana*

### The concept of guidelines

The most widely accepted definition of “guidelines” refers to: “... a set of recommendations systematically developed on the basis of acknowledgements continuously updated and validated, aiming to determine an optimal attitude to be adopted for a peculiar task. Guidelines should be considered as a starting point for setting attitudes and behaviors shared among different types of organizations, including private and public ones, belonging to different areas (including the medical setting), usually being *not mandatory* (conversely labeled as “protocols” or “procedure codes”), *but highly recommended*”<sup>1</sup>.

Medical guidelines usually represent a synthesis of current scientific knowledge developed by the integration of the evidence-based data (mainly from randomized, placebo controlled clinical trials, RCTs) with the rational clinical practice and the experience regarding a specific topic. Generally, guidelines are defined by a committee of internationally recognized experts on the topic, evaluating available data and ranking studies according to certain “levels of evidence”, i.e., the modality by which researchers categorize efficacy from evidence-based data. In addition, several committees incorporate adjunctive clinical data from open trials, retrospective analyses and expert consensus on efficacy and tolerability (in one word, effectiveness) of different treatment options in order to propose a “recommendation grade” for each therapeutic option<sup>2</sup>.

Guidelines should be particularly valuable when a given disorder manifests with heterogeneous clinical presentations and/or when it should require different therapeutic approaches within its course, as in the case of bipolar disorder (BD), which often represents a hard to treat, disabling, and potentially life threatening condition<sup>3</sup>.

Within the past decades, a growing number of guidelines have been proposed for the treatment and management of BD across its different phases; such guidelines are continuously updated and increasingly comprehensive. Yet, despite their informative and educational value, a number of constraints strongly limit their clinical applicability, actually making them difficult to be followed by

clinicians. We consider some aspects that may account for this issue, also trying to give practical advice about possible misleading use of the guidelines and their possible negative consequences in the treatment of BD in everyday clinical practice.

### Bipolar disorder guidelines: potential biases

From a pathogenic point of view, BD is probably a heterogeneous condition characterized by a complex clinical picture with extremely variable symptomatological presentation, course and outcome. Affective episodes such as (hypo)-manic, depressive and mixed states are usually intermixed with temperamental dysregulations, complex physical and psychiatric comorbidities and a large amount of possible complications<sup>4</sup>. Given the complexity of the disorder and the extreme variability of the presentations, most patients are diagnosed after 10-15 years from the first clinical manifestations<sup>5</sup>.

Depression, comorbidity and socio-relational problems are the most frequent reasons for treatment request, while mania is usually less commonly reported in clinical settings<sup>4</sup>. In particular, typical euphoric-grandiose mania is a very uncommon condition in clinical practice, whereas most manic patients are mixed, dysphoric, psychotic, aggressive, hostile and with lack of insight. This clinical reality is not only the major source of misdiagnosis (i.e., many patients receive for long periods diagnoses of depression, personality disorders, schizophrenia), but also the main reason for which treatment guideline are very difficult to be applied in everyday clinical practice.

Since 2005, many guidelines have been updated or revised. Among others, these include those of the World Federation of Societies of Biological Psychiatry (WFSBP)<sup>6,7</sup>, of the Canadian Network for Mood and Anxiety Treatments (CANMAT)<sup>8</sup>, of the International Society for Bipolar Disorders (ISBD)<sup>9</sup>, of the British Association for Psychopharmacology (BAP)<sup>10</sup> and of the National Institute for Health and Clinical Excellence (NICE)<sup>11</sup>. Considering the clinical relevance of BD and the progressively increasing number of treatment options, including both pharmacological

and non-pharmacological interventions, new guidelines and updates are continuously proposed.

While an in-depth discussion of single guidelines is out of the scope of this editorial, it may be remarked that they generally converge, essentially due to similar methodological approaches and to the fact that many international members belong to multiple committees at once. Additionally, major guidelines are not only evidence-based but also “evidence-biased”, essentially by commercial interests. These latter, other than influence the results of RCTs studies (sponsor bias), could make also some sponsored drugs more visible (or invisible in case of unfavorable outcomes and/or negative tolerability profiles) than others. Moreover, the difficulty of conducting large RCT studies without adequate financial support, especially for older agents with no more commercial interest, unbalances RCT evidences in favor of the most recent sponsored compounds.

Apart from potential commercial biases, the RCT model utilized for the study of BD treatments appears to be substantially inadequate and profoundly misleading (Table I). The intrinsic methodological limitations of RCTs are difficult to be applied to everyday clinical practice, especially due to sample selection and study design. The scenario of an “acute” patient population, yet able to provide a valid informed consent and to strictly adhere to the treatment protocol, achieving a very “high” placebo response, hardly resembles the real world clinical practice.

Most importantly, due to their relying on the evidence de-

rived from RCTs, treatment guidelines for BD are mainly focused on different phases of the illness such as acute mania (the best covered aspect), bipolar depression (the less covered, most controversial, issue) and maintenance treatment<sup>12</sup>. Mania and depression, however, are not independent affective states, and the treatment of the acute episodes has always long-term implications. In the natural course of many bipolar patients, mania immediately precedes depression and develops in it (actually patients do not suffer from mania but from a manic-depressive cycle), in others it follows depression and in most cases excitatory and depressive features are simultaneously present (mixed forms). The pharmacologic treatment of mania can precipitate depression, while in some other cases (especially “treatment-resistant” depression) improper pharmacological interventions could induce rapid-cycling or chronic mixed states<sup>13</sup>.

In fact, the higher the anti-manic or antidepressant effect of a certain drug, the higher its chance to induce or precipitate the opposite-polarity phase of the disorder and to destabilize the course of the illness. In this sense, typical antipsychotics, such as haloperidol or chlorpromazine, are very effective in controlling acute psychotic mixed-mania but are very likely to precipitate depression. Similarly, tricyclic antidepressants are more effective than second-generation antidepressants in treating severe melancholic depression, but are very likely to induce manic switch or mood instability. RCTs with new generation antipsychotics and antidepressants are not designed to explore these complications of the acute treatments, due to the short duration of the observation, the bias in the selection of the cases and the low number of subjects that complete the so called long-term trials. In this sense, the evidence of a more favorable tolerability profile reported for second generation antipsychotics or newer antidepressants versus their respective predecessors is very weak. Moreover, if a true different pattern of tolerability exists, it appears to be more quantitative rather than qualitative. In other terms, pharmacological treatments that are effective in controlling symptomatological aspects of the affective episodes (e.g., antidepressants and antipsychotics) may have a certain probability of worsening the basic illness. This appears to be a sensitive issue since, in fact, the complications of BD are usually more severe and difficult to treat than the basic illness, including those produced by drug treatment (rapid cyclicity, tardive dyskinesia, supersensitivity psychosis, etc.).

As concerns the selection among different drugs, guidelines focus more on quantitative (number of studies, effect size, response rates) rather than on qualitative differences (e.g., antipsychotics may act on different clusters of acute mania compared to lithium and other agents). A global reduction of the total score of a certain rating scale for acute mania (e.g., a Young Mania Rating Scale [YMRS]

**TABLE I.**

Potential biases associated with RCT methodology and with the current conceptualization of BD, as implicit in RCT. *Limiti potenziali della metodologia degli RCT e della concettualizzazione del BD negli RCT.*

1. Commercial bias
2. Sample bias
3. RCT study design
4. Mania and depression are not independent states (the episode in many cases is part of a cycle)
5. Mixed state, the most frequent presentation of BD, is ignored by RCTs
6. Manic, mixed or depressive states are the most eloquent manifestations of the disorder but do not fully characterize it (temperamental dysregulation, comorbidity, complications, etc.)
7. Antimanic or antidepressant treatments may precipitate the opposite phase or induce chronicity and long-term destabilization

score of  $\leq 12$  is often considered as the optimal cut-off defining remission in most of the RCT) does not necessarily imply a clinical reduction of the manic excitement and its possible associated psychotic features. For example, antipsychotics may acutely act more as “major tranquilizers” (or “neuroleptics”) rather than true antipsychotics (anti-delusional) compounds, and even when hostility and motor excitement are largely reduced, patients could still experience significant psychosis or poor insight of illness.

It is also unclear how long should clinicians wait before changing or amending medication; everyday practice cannot wait for one or two weeks in cases of severe acute mania or mixed state, as proposed by treatment guidelines.

Finally, in clinical practice, many BD patients are pharmacologically treated for decades with the consequence of complex adaptations to the pharmacological regimen (i.e., lithium discontinuation is associated with increased relapse rate, treatment resistance and suicidality<sup>14</sup>) that are still not fully understood. In very few RCTs does evidence rely on prolonged follow-ups (e.g., 52 weeks or more), thus being not really “long-term”, at least in the meaning of clinical practice.

These potential issues not only reduce the possibilities for clinicians to strictly adhere to BD guidelines, possibly explaining why up to 30-40% patients do not benefit from RCT evidence-based treatments, but also account for about 20-25% of treatments appearing inadequate or even harmful<sup>15</sup>.

## The problem of polypharmacy

In clinical practice, BD is a condition where polypharmacy, as well as nonpharmacological augmentation (e.g., psychotherapy and physical stimulations), is the rule rather than the exception. While some drug combinations are supported by clinical trials, many of them are reported to be of unproven efficacy, or even harmful. While doctors should perceive BD guidelines as being inappropriate for most severe cases, usually requiring more sophisticated treatment approaches, they could simply get “disoriented” or feel “left behind” when it comes to evaluate complex potential pharmacological interactions, thus increasing the risk for patients to receive inappropriate or even harmful treatments. Data derived from RCTs of drug combinations are virtually lacking, the evidence available is on add-on strategies, mainly focused on new generation antipsychotics on the top of classic mood stabilizers such as lithium or valproate. Monotherapy with mood stabilizers such as Lithium or Valproate appear to have in RCTs the same response rate as atypical antipsychotics, and better tolerability than combinations. In clinical practice these medications, because of their reduced efficacy and rapidity of response in the most severe “real world”

patients, are typically combined from the beginning with typical and atypical antipsychotics, antidepressants, benzodiazepines, depending on the phase of illness, potentially further reducing the clinicians’ entrusting with guideline directives. Most importantly, following the RCT-guidelines indications, atypical antipsychotics should be universally considered the first-choice treatment for every kind of mania or acute psychosis in general. Many patients with severe psychotic mania or mixed state (which have been never included in RCT, but are very common in clinical practice) may not fully respond to the atypical antipsychotics. In these cases, a widely diffuse and dangerous practice, sometimes favored by commercial interests, is the association of typical and atypical antipsychotics for protracted periods, with the consequence to expose BD patients to an increased risk of severe and potentially irreversible neurobehavioral, metabolic, and cardiologic side effects.

Similarly to the doctors, even patients may have difficulties in following BD guidelines. This may be essentially due to different factors, including the severity of the disease (including cognitively impaired cases) and its potential lack of insight, the still too high social stigma and consequent secrecy of BD, socio-economic barriers, and lack of knowledge about the guidelines by their care givers and physicians.

BD treatment guidelines have been defined as “unrealistic, but indispensable”<sup>2</sup>. In fact, they often do not account for real world contexts; severity and nature of the illness, co-morbidity, and polypharmacy are very different in clinical practice, as compared to the RCT setting. Different levels of evidence and different types of recommendations (e.g. efficacy, safety, experience, cost), indeed make current BD guidelines more reliable for accounting “what treatment to avoid” rather “which one to use”. Also, BD guidelines are mainly focused on newer agents rather than older compounds.

The principal recommendations given in guidelines usually apply to “ideal patients” who are enrolled in placebo-controlled trials. Due to the extreme variability of the presentations, clinical practice requires greater attention to the management of the complex situation of every single patient; in this context, it is very difficult to reduce treatment variability and to promote expert consensus based on “unrealistic” evidence. All the available drugs, old and new, are not the specific treatment for mania, depression, psychosis and BD, but are characterized by many biological effects that, incidentally, could improve some aspects of the illness; their cost/benefit ratio should be evaluated in every clinical situation, considering different subtypes of mania and depression, paying greater attention to mixed states, previous pharmacological treatments and current polypharmacy, especially in the acute setting. Finally, clinical practice should be able to consid-

er the true course of the disorder, which is not “episodic” but “cyclic”, “unstable”, and in many cases associated with complications, “cognitive deterioration” and individual sensitivity to different drugs, in terms of treatment response and side effects.

In conclusion, BD evidence-based guidelines provide important informative and educational contribution and may be very useful to investigators and clinicians in order to improve the medical care of these patients; however, to achieve this ambitious goal, a confident use is recommended, essentially acknowledging their points of strength, but, overall, their possible limitations.

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