

Treatment guidelines for bipolar disorder: a bit unrealistic, but indispensable

Linee guida per il trattamento del disturbo bipolare: poco realistiche, ma indispensabili

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Summary

Treatment guidelines for bipolar disorder may represent useful tools in choosing appropriate treatments, evaluating the role of specific interventions in the management and for following-up an illness, and evidence of the usefulness of their implementation has been produced.

Guidelines cannot replace clinical knowledge that aims to improve patient health globally. However, guidelines remain a point of reference when they merge efficacy, safety and tolerability (which, combined together, constitute what we term effectiveness).

A priority in the development of future guidelines and updates, should be a reader-friendly organization of the document, with clear algorithms and with limited dispersion of information allowing the better dissemination and implementation.

Key words

Bipolar disorders • Treatment guidelines • Evidence based medicine • Experience-based medicine

Riassunto

Le linee guida al trattamento del disturbo bipolare possono rappresentare strumenti utili per la scelta di trattamenti appropriate, per la valutazione del ruolo di interventi specifici nella gestione di una malattia e per il suo follow-up; evidenze dell'utilità della loro attuazione sono state già ottenute.

Le linee guida non possono sostituire la conoscenza clinica che mira a migliorare globalmente la salute del paziente. Tuttavia, le linee guida rimangono dei punti di riferimento quando combinano efficacia, sicurezza

e tollerabilità (che nell'insieme costituiscono l'efficacia nel mondo reale).

Una priorità nello sviluppo di linee guida ed aggiornamenti futuri sarebbe l'organizzazione del documento in modo da facilitare il lettore, con algoritmi chiari e dispersione dell'informazione limitata, che consenta la loro migliore diffusione e realizzazione.

Parole chiave

Disturbi bipolari • Linee guida al trattamento • Medicina basata sull'evidenza • Medicina basata sull'esperienza

Treatments guidelines: what for?

Guidelines are systematically derived statements that are aimed at helping individual patient and clinician decisions. They represent a synthesis of current scientific knowledge developed by integration of the evidence-based data (from randomized clinical trials, RCTs) with the rational clinical practice and experience regarding a specific topic.

In general, the process by which a guideline is generated begins with a committee of experts who undertake an evaluation of the existing data ranking studies according to certain Levels of Evidence,

which represent the modality by which researchers categorize efficacy from evidence-based data. By incorporating adjunctive clinical data from open trials, retrospective analyses, case reports and expert consensus in clinical experience and additional clinical aspects (safety, tolerability and effectiveness) a Recommendation *Grade* is then proposed for each compound.

The growing bulk of knowledge on epidemiological, clinical, therapeutic aspects of bipolar disorder (BD) underpins a need for up-to-date instruments which may help clinicians in managing different aspects of this complex illness. Within the past ten years, a number of guidelines and expert consen-

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sus have been developed to increase awareness of the misdiagnosis of BD and the growing number of potential treatments, mainly pharmacological, but also, more recently, psychological and physical¹⁻⁹.

The year 2009 has brought a great deal of consensus, insight, and indications on how to best treat people with BD, with newly published updates and new treatment guidelines. This blooming may be greatly justified by the important treatment developments during the past 5 years which had an impact on how BD treatment needs to be approached¹⁰, and the subsequent need for a theoretical and methodologically solid systematization.

Main bipolar disorder treatment guidelines

The majority of the most influential treatment guidelines published their updates and revised versions during 2009. The *British Association of Psychopharmacology* (BPA) revised their guidelines⁵ with an updated version¹¹. The Canadian guidelines were published originally in 2005 and updated by the end of 2006¹². The new update has been opened to international experts designed by the *International Society of Bipolar Disorders* (ISBD), thus becoming the first ISBD-endorsed treatment guideline. Compared to the previous editions, it contains important changes in recommendations for the treatment of mania,

TABLE I.

Summary of treatment recommendations for acute mania. *Riassunto delle raccomandazioni per il trattamento della mania acuta.*

Guidelines	BAP (British Association for Psycho-pharmacology)	CanMAT and ISBD (Canadian Network for Mood and Anxiety Treatments and International Society for BD)	NICE (National Institute of Clinical Excellence)	WFSBD (World Federation of Societies of Biological Psychiatry)
Reference	Goodwin et al., 2009 ¹¹	Yatham et al., 2009 ¹³	NICE, 2009 ¹⁵	Grunze et al., 2009 ¹⁶
1 st line	Not on treatment: VPA, AAPs Less severe: VPA, AAPs, Li, CBZ On treatment with Li: add AAP	- Li or VPA or AAPs (OLZ, RSP, QTP, QTP XR, ARP, ZIP) - Li/VPA + RSP or QTP or OLZ or ARP	Not on treatment: Severe mania: AAPs (QTP, OLZ, RSP) Less severe: Li or VPA On treatment: AAP+Li/VPA or Li/VPA + AAP	- Li or VPA or AAPs (ARP, OLZ, RSP, QTP, ZIP) - Li/VPA + AAP
2 nd line	- Li/VPA + AAPs - CLZ	- CBZ, PAL, Li or VPA + asenapine, Li + CBZ <i>Others:</i> - Hal, chlorpromazine, CLZ, OXC, tamoxifen, Li/VPA + Hal	Li/VPA + AAPs	- CBZ, Li + VPA, PAL, asenapine, Li + asenapine <i>Others:</i> - Hal, chlorpromazine, Li/VPA + Hal, Li + CBZ, CLZ, OXC, tamoxifen
Non pharmacological	2 nd line: ECT	2 nd line: ECT	- 2 nd line: ECT - Scarce evidence on rTMS	2 nd line: ECT Not recommended: rTMS
Not recommended	-	- LMT, gabapentin, topiramate, verapamil, tiagabine, RSP+ CBZ, OLZ + CBZ	- CBZ, LMT, gabapentin, topiramate monotherapies	Monotherapy: gabapentin, topiramate, LMT, verapamil, tiagabine

CBZ: carbamazepine; Li: lithium; LMT: lamotrigine; VPA: valproate; AAP: atypical antipsychotic; ARP: aripiprazole; CLZ: clozapine; OLZ: olanzapine; QTP: quetiapine; PAL: paliperidone; RSP: risperidone; ZIP: ziprasidone; Hal: haloperidol; ECT: electroconvulsive therapy; rTMS: transcranial magnetic stimulation.

TABLE II.

Summary of treatment recommendations for Acute Bipolar Depression. *Riassunto delle raccomandazioni per il trattamento della depressione bipolare acuta.*

Guidelines	BAP (British Association for Psycho-pharmacology)	CanMAT and ISBD (Canadian Network for Mood and Anxiety Treatments and International Society for BD)	NICE (National Institute of Clinical Excellence)	WFSBD (World Federation of Societies of Biological Psychiatry)
Reference	Goodwin et al., 2009 ¹¹	Yatham et al., 2009 ¹³	NICE, 2009 ¹⁵	Grunze et al., 2010 ¹⁶
1 st line	Severe: ECT Moderate: - QTP/LMT/Li/VPA - SSRIs or other (not TCA, + Li/DVP, AAP if BD I) Less severe: QTP, LMT If no mania: Ads	- Li or LMT or QTP - Li/VPA/OLZ + SSRI - Li + VPA - Li/VPA + bupropion Bipolar II depression: QTP	AM + SSRIs Li/AC + QTP Add LMT If psychosis: Add AAPs (OLZ, QTP, RSP)	- QTP, adj QTP - OLZ, OFC - LMT + Li
2 nd line	Adj TCA ECT	- QTP+SSRI, DVP, Li/VPA + LMT - Add modafinil Bipolar II depression: monotherapy with Li, LMT, VPA Combination: Li/VPA + ADs, AAP + ADs, Li + VPA	Adj LMT; ADs switch to: mirtazapine, venlafaxine Adj: QTP or OLZ or Li	Li, CBZ, LMT AAPs ECT Li/VPA + ADs
Non pharmacological	2 nd line: ECT, CBT, FFT	2 nd line: ECT	- 2 nd line: ECT, adj individual, group psychotherapy including psychoeducation	2 nd line: ECT
Not recommended	-	- LMT, gabapentin, topiramate, verapamil, tiagabine, RSP+ CBZ, OLZ+CBZ	- VPA, CBZ, LMT gabapentin, ADs monotherapy	ADs monotherapy

Ads: antidepressants; SSRI: Selective Serotonin Reuptake Inhibitors; TCA: tricyclic antidepressants; AM: antimanic agent; CBZ: carbamazepine; Li: lithium; LMT: lamotrigine; VPA: valproate; AAP: atypical antipsychotic; ARP: aripiprazole; CLZ: clozapine; OLZ: olanzapine; QTP: quetiapine; PAL: paliperidone; RSP: risperidone; ZIP: ziprasidone; Hal: haloperidol; ECT: electroconvulsive therapy; rTMS: transcranial magnetic stimulation; CBT: cognitive behavioural therapy; FFT: family focused therapy; Adj: adjunctive.

bipolar depression, and maintenance, as well as for bipolar II disorder ¹³. The NICE (*National Institute for health and Clinical Excellence*) published its first version of the guidelines for bipolar disorder in 2006 ¹⁴ but also have presented their updated version ¹⁵. Finally, the *World Federation of Societies of Biological Psychiatry* (WFSBP) has designed a Task Force to work on their new bi-

polar treatment guidelines version. The original ones were published in 3 separate papers addressing bipolar depression, mania, and maintenance therapy, in the *World Journal of Biological Psychiatry* in 2002, 2003, and 2004, respectively ²⁻⁴. Their updated versions have been published starting from acute bipolar depression ¹⁶, then with acute mania ¹⁷ and the maintenance

TABLE III.

Summary of treatment recommendations for Maintenance Treatment (WFSBD guidelines are not included). *Riassunto delle raccomandazioni per il trattamento di mantenimento (le linee guida della WFSBD non sono incluse).*

Guidelines	BAP (British Association for Psycho-pharmacology)	CanMAT and ISBD (Canadian Network for Mood and Anxiety Treatments and International Society for BD)	NICE (National Institute of Clinical Excellence)
Reference	Goodwin et al., 2009 ¹¹	Yatham et al., 2009 ¹³	NICE, 2009 ¹⁵
1 st line	Mania predominates: - Li, ARP, QTP, VPA, OLZ Depression predominates: - QTP, LMT	Monotherapy or adj with: Li, ARP (for mania), LMT (limited efficacy in preventing mania), VPA, OLZ, QTP, RLAI, Li/DVP + QTP, adj ZIP Bipolar II: Monotherapy or adj: Li or LMT	- Li, VPA, OLZ Recent mania: - Li or VPA No recent mania: - LMT or QTP, LMT + AM, adj ADs (if depressive symptoms) Rapid cycling: Li + VPA
2 nd line	Predominantly manic - CBZ, Li/VPA + AAP Predominantly depressive: - Li, LMT+AAP Bipolar II - LMT or QTP CLZ in resistant patients	CBZ, Li/VPA - Li + CBZ/RSP/LMT, Li/VPA + OLZ, OLZ + FLX Bipolar II: VPA, Li/VPA+ADs, two out of Li/VPA/LMT/AAP	Combination: - Li, VPA, OLZ Recent mania: - ARP, OLZ, CBZ, CLZ, ECT Recent depression: - Li, ADs+AM, OFC, QTP, LMT, Rapid cycling: Li, Li/VPA+LMT
Non pharmacological	2 nd line: ECT, CBT, FFT	Adj CBT or psychoeducation	2 nd line: ECT, adj individual, group psychotherapy including psychoeducation
Not recommended	-	Adj flupenthixol Monotherapy: ADs gabapentin, topiramate	VPA in women Monotherapy: CBZ, LMT, gabapentin, topiramate

Ads: antidepressants; SSRI: Selective Serotonin Reuptake Inhibitors; TCA: tricyclic antidepressants; AM: antimanic agent; CBZ: carbamazepine; Li: lithium; LMT: lamotrigine; VPA: valproate; AAP: atypical antipsychotic; ARP: aripiprazole; CLZ: clozapine; OLZ: olanzapine; QTP: quetiapine; PAL: paliperidone; RSP: risperidone; ZIP: ziprasidone; Hal: haloperidol; ECT: electroconvulsive therapy; rTMS: transcranial magnetic stimulation; CBT: cognitive behavioural therapy; FFT: family focused therapy; Adj: adjunctive.

ones, which have not been published at the time of writing this article.

Recommendations from the different guidelines are systematically summarized for acute mania, acute bipolar depression and maintenance treatment respectively on Tables I, II, III.

The importance of guidelines despite their shortcomings

Guidelines may represent useful tools in choosing appropriate treatments, evaluating the role of specific interventions in the management and follow-

up of an illness, and evidence of the usefulness of their implementation has been produced^{18,19}. In the very case of BD, the increasing data on different pharmacological, psychological and biophysical interventions require standardization in the treatment management, as well as an operationalization into clinical practice which may be hard to be translated directly from each and every RCT. Guidelines have been developed in order to respond to this need, to order and summarize results by furnishing treatment algorithms.

Most importantly, treatment guidelines are a useful instrument to inform clinicians about what *not*

to do within clinical practice. This may have very positive consequences in the quality of the care furnished to patients, by limiting dangerous trends or highly subjective evaluations in the use of therapies with questionable efficacy.

Apart from the benefits for the patients, recommendations may be needed to backup clinicians' decision with theoretical support from official and international societies and expert opinions, something which, in times of defensive medicine, may have practical importance.

Guidelines have, though, several shortcomings: they are *evidence-based*, but also *evidence-biased*, because the available evidence is biased by commercial interest. While commercial interest cannot change the results of a randomized, double-blind trial, the fact that only some studies are sponsored makes some compounds more visible than others. In the case of bipolar disorder, we miss studies on specific compounds, such as clozapine or amisulpride, we miss more head-to-head trials comparing antipsychotics, and we miss reliable data on antidepressants. Guidelines get outdated quite quickly and often do not take into account the specific particularities of the country or the mental health system where they are supposed to be implemented. Hence, cost-effectiveness of treatment options is an element of key importance in the organization of the health system. When possible, cost-effective solutions should be preferred and implemented, and this represents another topic on which guidelines may, to some degree, help quite significantly, although they need to be adapted to the local policies.

Bridging the gaps between Evidence-based and Experience-based Medicine

According to several commentators clinical freedom, the art of medicine, and, by implication (as a consequence), some degrees of patients' welfare, are threatened by Evidence Based Medicine (EBM) ²⁰. Since EBM has developed over the last decades, claims about a better evidence for medical treatments and improvements in healthcare delivery have been matched by a growing criticism on EBM's reductionism and uniformity, its problematic application to individual patients, and its alleged denial of a continuing need for clinical interpretation, insight, and judgment ²¹.

Most of the criticism against EBM and the development of Clinical Guidelines is based on reduction-

ism of Randomized Clinical Trials (RCT) that have been conducted in a biased clinical population with a higher number of drop-outs, a higher placebo response together with several other methodological shortcomings.

The art and science of medicine are more conceptually and practically connected than defenders of clinical freedom, whatever they conceive that to be, are willing to admit. Clinical guidelines are only as good as evidence and judgments they are based upon ²².

Although generally acknowledged, heterogeneity of bipolar disorders is not taken into consideration/account in the current treatment guidelines. A comprehensive historical, familial and psychopathological assessment cannot be incorporated into clinical guidelines; nevertheless, it should be integrated into treatment decision leading to a targeted treatment ^{23 24}. Individual factors make the difference in decision making process; thus, the expert clinician has to make clinical synthesis of the 'best evidence' available within the individual patient needs ²⁵. This increasingly wider range of therapeutic options both for the primary and comorbid conditions needs to be dealt with an appropriate psychoeducational framework without overpromising immediate therapeutic benefit or ultimate symptom remission.

A considerable amount of polypharmacy and polypsychotherapy may be required to match the complexity of bipolar presentations and comorbidities ²⁶. While some of these combinations are supported by clinical trials, many of them are of unproven efficacy. These trends put patients at increased risk of drug-drug interactions with uncertain gains in terms of quality of care and clinical outcomes ²⁷. Although lithium monotherapy might appear to have a higher rate of response, this medication is typically given in conjunction with other agents, such as antidepressants, antipsychotics, benzodiazepines, thyroid medications, and multivitamins. The ideal drug would present low risk of interaction with mood stabilizers and a cardiovascular profile generally well-tolerated.

Other misconceptions derive from approval processes from regulatory agencies, in which approval is based on the ability of the active drug to exceed the efficacy of placebo, not on the achievement of a preset clinically robust standard, as desired by most clinicians. Second, and related to this point (item), a success rate of 50% is used in most analy-

ses, and only rarely major consideration is given to the desired endpoint of remission. Finally, FDA registration, with the sole exception of lamotrigine, has been based on approval for the acute treatment of mania rather than long-term outcome.

Therefore, it is clear that approval of a drug for monotherapy is not synonymous with the establishment of sufficient efficacy against all therapeutic targets that ac clinicians/physicians seek for patients with bipolar disorder. Given the complexity of the disorder and the goal of achieving and maintaining remission, it appears that polypharmacy and complex combination therapy are often required to fulfill this mission^{28,29}. For example, a drug such as topiramate, which is not effective in the treatment of acute mania in adults, may, nonetheless, be helpful in comorbid alcohol use, cocaine use, PTSD, eating disorders, and obesity.

Another relevant issue is 'off-label' prescription³⁰. Physicians' freedom to prescribe drugs off-label carries (brings, has) important advantages. It permits innovation in clinical practice, particularly when/if approved treatments have failed (have been failing). It offers patients and physicians an earlier access to potentially valuable medications and allows physicians to adopt new practices based on emerging evidence. It can provide the only available treatments for/in case of "orphan" conditions. At the same time, (the use of) off-label (use) has potentially negative consequences: it undercuts expectations that drug safety and efficacy have been fully evaluated. Health care costs tend to increase if newer and more expensive drugs are used off-label, it increases³¹. For example, no mood stabilizers have been approved for bipolar II disorder, but only for bipolar I symptoms. This does not mean that these medications are inappropriate for bipolar II: manufacturers have simply not bothered to seek such an indication. As a result, virtually all medications used for bipolar II – such as lithium, valproate, lamotrigine, and many/several others – are prescribed off-label.

In most other chronic or recurrent medical disorders, combination treatment is not only widely practiced, but also the standard of care. One only needs to think of/about the multiple medications for cancer, heart disease, and rheumatoid arthritis to see that polypharmacy for patients with bipolar disorder is not unconventional but typical (widely used in) of/in many other disorders.

Further researches would be very helpful in clarifying many remaining questions/items concerning indications and long-term effects of specific psychosocial and rehabilitative interventions; in quantifying costs and benefits of particular methods or combinations; finally in suggesting rational bases for selecting particular approaches for individual patients. Such information is particularly important for (those) efforts to balance current market forces tending to overvalue the considerable – but limited – benefits of medication alone and to redress a growing imbalance between biomedical and psychosocial approaches in contemporary psychiatric therapeutics.

Clinical guidelines are only one option for improving the quality of care. Too often, their advocates view guidelines as a "magic bullet" for healthcare problems and ignore more effective solutions. Clinical guidelines make sense when practitioners are unclear about appropriate practice and when scientific evidence can provide an answer.

Guidelines cannot replace clinical knowledge aiming to improve the patient's general health. However, guidelines remain a point of reference when they merge efficacy, safety and tolerability (effectiveness). For example, WFSBP guidelines consider aripiprazole and ziprasidone as first choice treatment in bipolar mania, since these AAP have shown a strong efficacy without provoking/arising significant tolerability issues¹⁶.

Finally, healthcare systems and payers may be harmed by following guidelines if utilization escalates, operating efficiency is compromised, or limited resources are wasted³². Some clinical guidelines, especially those developed by medical groups or other groups unconcerned about financing, may advocate costly interventions that are unaffordable or that could lead to cut resources needed for more effective services.

Shortcomings and development(s)

In the face of these mixed consequences, attitudes about whether clinical guidelines are good or bad for medicine vary from one group to another. Guidelines produced by governments or payers to control spiraling costs may constitute responsible public policy but may be resented by clinicians and patients as an invasion of personal autonomy. Guidelines developed by specialists may seem self

serving, biased, and threatening to generalists. To specialists, guidelines developed without their input do not contain adequate expertise)³³.

Evidence-based medicine, like other models of care, has limitations. In particular, efforts need to be directed toward improving clinicians' access to evidence at the point of care; developing better methods of describing evidence to patients in order to facilitate shared decision-making³⁴.

Many questions in medical research are investigated in observational studies: much of the research into the cause of diseases relies on cohort, case-control, or cross sectional studies. Observational studies also play a role in researching into the benefits and harms of medical interventions. Randomised trials cannot answer all important questions about a given intervention. For example, observational studies are more suitable to detect rare or late adverse effects of treatments, and are more likely to provide an indication of what is achieved in daily medical practice.

The best medical practice is similar neither to baroque nor grunge music; instead, it is like good jazz, combining technical mastery with the artistry of focused personal improvisation. Clinical jazz combines the structure supplied by patient-oriented evidence with the physician's clinical experience in order to manage situations of uncertainty, instability, uniqueness, and conflicting values³⁵.

Conclusions and future steps

A priority in the development of future guidelines and updates, should be a reader-friendly organization of the document, with clear algorithms and with limited dispersion of information.

The principal recommendations given in guidelines usually apply to *ideal patients*, who are those who are enrolled in the placebo-controlled trials that qualify for the highest levels of evidence. To bridge the gap between research and clinical practice, future guidelines should also focus on different subpopulations of patients affected by BD, with particular attention to mixed episode³⁶, and rapid cycling³⁷, who are not adequately studied, and address the management of comorbidities, even if evidence is limited.

From a methodological point of view, results from double-blind, placebo-controlled trials are sup-

posed to be more valid than those of less rigorous observational studies, but, practically, open randomized and large observational studies can be as accurate as level I studies while having the advantage to be more generalizable and near to "every-day clinical practice"³⁸. For this reason it also appears crucial that large, prospective trials in unselected populations be conducted and considered in treatment guidelines, in order to improve evidence-based data and to increase the confidence that a given evidence based treatment is also effective in real word settings.

Another change that should be operated in treatment research is the attitude towards negative trials, and this is obviously reflected by guidelines, which represent the mirror of current clinical research. Publication bias is a serious problem which may be improving lately, and which could lead to a more objective resizing in the recommendation grade of some compounds as a consequence.

Clinicians face the everyday challenge to treat patients with bipolar disorder, a difficult illness because of its intrinsic complexity and variability. Guidelines cannot take into account its highly variable presentation, so they should be seen as not prescriptive, flexible tools. However, they may be very useful to reduce the sometimes unnecessary variability of clinical practice, and to help clinicians to avoid mistakes and the use of non scientific options. Clinicians have to integrate whatever type of recommendation from guidelines with experience, common sense, and respect for patients' choices.

Conflicts of Interest

Prof. Eduard Vieta has been a consultant for, received grant/research support, and honoraria from and been on the speakers/advisory boards of Almirall, Astra-Zeneca, Bristol-Myers-Squibb, Eli Lilly, Forest Research Institute, Geodon Richter, Glaxo-Smith-Kline, Janssen-Cilag, Jazz, Lundbeck, Merck Sharpe and Dohme, Novartis, Otsuka, Pfizer, Pierre-Fabre, Sanofi-Aventis, Servier, Schering-Plough, Takeda, and United Biosource Corporation.

Prof. Alessandro Rossi has received funding to attend national and international congresses and conferences and/or has served as a speaker or on advisory boards for Pfizer, Janssen-Cilag, Bristol-Myers-Squibb e Boehringer-Ingelheim.

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