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Editorial

EDITORIAL

Treatment Guidelines in Bipolar Disorders and the Importance of Proper Clinical Trial Design

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A working group led by Dr. Konstantinos Fountoulakis developed the first International College of Neuropsychopharmacology (CINP) clinical guidelines for the treatment of Bipolar Disorders in adult patients. Their work is very thoroughly described in four separate papers (parts) included in this issue of the journal. The first article is Background and Methods of the Development of Guidelines (Fountoulakis et al., 2017d); part 2 is Review, Grading of the Evidence, and a Precise Algorithm (Fountoulakis et al., 2017c); part 3 is The Clinical Guidelines (Fountoulakis et al., 2017a); and Part 4 is Unmet Needs in the Treatment of Bipolar Disorder and Recommendations for Future Research (Fountoulakis et al., 2017b).

The background section provides a very comprehensive historical review of bipolar disorder going back 5000 years, including its natural course of illness, phenomenology, and development of treatments.

The CINP guidelines are unique, as they include additional recommendations for specific clinical characteristics such as agitation, predominant polarity, mixed features, and rapid cycling course. Furthermore, guidelines are also provided for nonpharmacological treatments.

The authors clearly describe their approach on grading articles from the scientific literature, and methods for the development of guidelines. The guidelines were developed by an evidence-based consensus approach primarily based on placebo or active comparator randomized controlled trials (RCTs) but also taking into consideration posthoc analysis reports, related meta-analyses, and other treatment guidelines as well as the research and clinical expert opinion of the authors utilizing a Delphi method to reach final decisions.

The PRISMA method was used in the literature search (Fountoulakis et al., 2017d). The authors based their recommendations on 569 articles containing RCTs, reviews, posthoc secondary analyses or meta-analyses, and 57 publications on treatment guidelines. The authors searched MEDLINE (http://clinicaltrials.gov and http://www.clinicalstudyresults.org) as well as web pages of pharmaceutical companies with compounds used in bipolar disorder up to March 25, 2016.

The authors provide a critical analysis of the existing treatment grading methods that led them to determine that there was no optimal method to grade treatments for bipolar disorder, therefore creating their own grading system. Their methodology provides 32 different levels of recommendations, starting with the optimal: "At least 1 positive 2 active arm RCT vs placebo exists, plus positive 1 active arm RCTs, and no negative RCTs." Lower level scenarios take into account posthoc reports, meta-analyses, and failed trials. Different scenarios are ranked appropriately, as a different weight is given to the absence of evidence than to the presence of negative data.

A 5-level composite treatment recommendation was created that combines efficacy and safety/tolerability, which is a thoughtful approach. An important and reasonable consideration made by the group was to give a higher weight for safety than for efficacy. For instance, a level 1 recommendation requires level 1 for safety/tolerability but can include level 1 or 2 for efficacy. This can lead to treatments of superior efficacy but lower tolerability being ranked lower; level 5 is reserved for "not recommended."

Guidelines are provided for each of the major phases of bipolar disorder; a novel approach is emphasizing the importance of considering the maintenance phase when treatments are recommended during the acute phases.

Comparisons with recommendations of other bipolar disorder treatment guidelines (NICE, CANMAT/ISBD, WFSBP, and BAP) will be helpful to the reader.

Part 4, Needs in the Treatment of Bipolar Disorder and Recommendations for Future Research, is particularly thoughtful. The authors highlight the need to merge guidelines of all phases into a single guideline taking into consideration the course and staging of the condition. Furthermore, the authors

emphasize that current treatment guidelines encourage the fragmentation of bipolar disorder into phases resulting in the lack of an overall longitudinal therapeutic strategy. They also mention other areas of need for more evidence-based treatments, including use of combinations treatment and treatments for specific conditions such as mixed features or rapid cycling course.

The Value of Optimal Methodology in the Evaluation of Clinical Trial Results

The authors address a number of research design issues that need to be considered in the future development of treatment guidelines in bipolar disorder. A key point raised by the workgroup is the importance of the release of raw clinical trial data from industry to the scientific community. The value of this issue can be exemplified by a recent development of novel analyses of exiting longitudinal data such as the Multi-Outcome Analysis of Treatments that provides more pragmatic information for clinicians and investigators in guiding maintenance treatment decisions in bipolar disorder (Bowden et al., 2016; Tohen et al., 2016). The development of this methodology was possible as 3 major pharmaceutical companies provided the raw data to independent academic investigators who obtained a grant from NIMH (RC1MH088431, MTohen [PI]). The methodology is now available to the public (www.moatsofware.com; https://delta.uthscsa.edu/moat).

Another important issue raised in the guidelines is the need to develop uniform clinical trial standards including uniform results of outcomes to be reported. The authors provide helpful appendices with recommendations. To address this issue, The International Society for Bipolar Disorders recently proposed a uniform nomenclature for the definition of commonly used outcomes such as recovery, relapse, and remission (Tohen et al., 2009). In terms of suggested outcomes, the guidelines appropriately highlight the need to focus more on functional rather than symptomatic outcomes, an issue that has been raised in the literature (Dion et al. 1988; Goetz et al. 2007; Tohen et al. 1990, 2003).

An important recommendation by the workgroup is the need to report results on individual items in symptom rating scales in addition to overall results, which no doubt provides a better understanding of the specific benefits of a treatment; for example, in a patient with bipolar depression, the improvement of insomnia due to somnolence does not have the same value as the improvement of depressed mood.

The authors recommend statistical analyses of side effects; however, this has the potential to be misleading. With some exceptions (Zajecka et al., 2003), the sample size of the vast majority of clinical trials is determined by a power analysis to detect a difference (if one exists) for efficacy but not for safety (Tohen, 2013). Lack of proper sample size estimation can lead to a type II error where, due to a small size, the results fail to show that there is a difference in safety of a treatment compared with placebo when in reality there is a difference. Such a finding can lead to the dangerous conclusion that a treatment is safe when in reality it may not be.

Adequate sample size estimation is also essential in the interpretation of comparative studies of active treatments. Low statistical power due to a small sample size can lead to a type II error that concludes that two treatments are equally effective when in reality one is more effective than the other (Tohen, 2008, 2015).

In the interpretation of clinical trials, issues that need to be taken into account include potential observation bias (Tohen, 1992), the duration of the observation time for maintenance studies (Tohen, 2015), the selection of the patient population (Baldessarini et al., 2008; Tohen, 2012), and factors that lead to placebo response (Yldiz et al., 2007). Another potential source of bias that needs to be considered is funding source (Paul and Tohen, 2007; Tohen, 2007).

An area that in general receives little attention in treatment guidelines are cultural issues or differences in efficacy or tolerability across global populations to specific treatments (Gallo and Tohen, 2010; Tohen, 2014). Considering that CINP is a global organization, for its next version it should consider addressing this important issue as well as expanding the geographical diversity of the authors, as currently only Western Europe and Canada are represented with the omission of any authors from developing countries or East Asia.

Another important issue highlighted by the authors is the need to have more effectiveness studies. Treatment guidelines in general do not consider effectiveness comparison studies. An example of a well-designed effectiveness study is a recent head-to-head study comparing quetiapine vs lithium in the treatment of all phases in bipolar disorder under usual and customary clinical care conditions (Nierenberg et al., 2016).

In summary, CINP should be commended for the product of this distinguished group of experts that provides clinicians worldwide an opportunity to make evidence-based treatment decisions in the treatment of bipolar disorder that hopefully will result in improving the lives of those who suffer from this devastating condition.

Statement of Interest

Dr. Tohen was a full-time employee at Lilly (1997–2008). He has received honoraria from or consulted for Abbott, Alkermes, Allergan, AstraZeneca, Bristol Myers Squibb, Elan, Forest, Geodon Richter Plc, GlaxoSmithKline, Johnson & Johnson, Lilly, Lundbeck, Merck, Minerva, Neurocrine, Otsuka, Pamlab, Pfizer, Roche, Shire, Sunovion, Teva, Wyeth, Elsevier Publishing, and Wiley Publishing. His spouse was a full-time employee at Lilly (1998–2013).

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