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Treatment of Bipolar Disorders with Second Generation Antipsychotic Medications



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Care and Treatment in Psychiatry

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The recognition, diagnosis and treatment of bipolar disorders (BD) is a major task for public health and for mental health authorities. Bipolar disorders are among the most common mental disorders with a prevalence estimated at 1.5% of the adult population. When the whole spectrum of bipolar disorders including their sub-threshold forms are taken into consideration, the rate of BD has been estimated by some authors to be as high as 6%. The fact that BDs are recurrent makes the provision of effective and well-tolerated treatment to those suffering from these disorders even more important.

Pharmacological treatment is central to the care of patients suffering from BD. Ideally, such treatment should rely on drugs that have few if any side effects and which are:

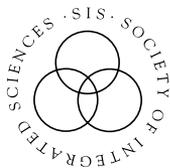
- effective in the treatment of acute manic symptoms and syndromes
- effective in the treatment of bipolar depression
- effective in the maintenance treatment of BD

As none of the currently available mood-stabilizers fulfill all of these criteria, clinicians have welcomed the results of studies that showed that second generation antipsychotic medications (SGAMs) can be useful in the treatment of various forms of bipolar disorders.

This review focuses on the evidence of the effects of SGAMs on BD. It is presented fully cognizant of the fact that the treatment of people with BD is a complex process that involves the participation of patients, their families and health and other social service workers. Psychopharmacotherapy plays an important role in this process, but should be seen as a part of the total treatment plan rather than as being sufficient by itself.



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1. Introduction

by Marek Jarema and Norman Sartorius

The recognition, diagnosis and treatment of bipolar disorders (BD) is a major task for public health and for mental health authorities. Bipolar disorders are among the most common mental disorders with a prevalence estimated at 1.5% of the adult population (Weissman et al. 1996). When the whole spectrum of bipolar disorders including their sub-threshold forms are taken into consideration, the rate of BD has been estimated by some authors to be as high as 6% (Judd and Akiskal, 2003). The fact that BDs are recurrent makes the provision of effective and well-tolerated treatment to those suffering from these disorders even more important.

Pharmacological treatment is central to the care of patients suffering from BD. Ideally, such treatment should rely on drugs that have few if any side effects and which are:

- ◆ effective in the treatment of acute manic symptoms and syndromes
- ◆ effective in the treatment of bipolar depression
- ◆ effective in the maintenance treatment of BD

As none of the currently available mood-stabilizers fulfill all of these criteria, clinicians have welcomed the results of studies that showed that second generation antipsychotic medications (SGAMs) can be useful in the treatment of various forms of bipolar disorders.¹ (Mensiunk and Slooff, 2004).

¹ Olanzapine, risperidone and quetiapine have been approved in acute mania indications, olanzapine has been approved for the maintenance treatment of BD and the combination olanzapine with fluoxetine has been approved for the treatment of bipolar depression (Ketter et al. 2004).

However, the introduction of SGAMs into the treatment arsenal raises several important questions:

- Will treatment with SGAMs reduce the numbers of therapy resistant forms of BD?
- Does the success of the treatment of BD with SGAMs ex juvantibus re-open the question of whether it is justified to consider all psychotic illness as a single nosological category (the unitary psychosis, Einheitspsychose) rather than a group composed of two sub-groups – the affective psychosis and the schizophrenic psychoses?
- Can the results of investigations into the usefulness of SGAMs in the treatment of BD obtained in the first set of studies be confirmed by further studies in the same settings and in studies in other countries with a different climate, different dietary habits and different cultural traditions?
- What ethical issues arise because of the introduction of new treatment options which will – in part because of their higher costs – not be equally available to all patients suffering from BD?
- What proportion of mental health budgets should be reserved for in-service training for different categories of health personnel in the use of SGAMs?
- What system of monitoring experience can be put in place to ensure that the results of treatment under real life circumstances are examined and used in the development of guidelines for the administration of medications in different settings?

The answers to these questions will have to come from research and from a systematic exploration of the experience obtained using SGAMs: the first and preparatory step of this process is the systematic and critical review of the available evidence on the effects and patterns of use of SGAMs. The critical review that is given in the chapters of this volume aims to serve that purpose

and facilitate teaching, research and the analysis of evidence in the use of SGAMs in the countries of Central Europe.

This review focuses on the evidence of the effects of SGAMs on BD. It is presented fully cognizant of the fact that the treatment of people with BD is a complex process that involves the participation of patients, their families and health and other social service workers. Psychopharmacotherapy plays an important role in this process, but should be seen as a part of the total treatment plan rather than as being sufficient by itself.

The review is divided into chapters which deal with various aspects of BD treatment: acute mania, bipolar depression, maintenance treatment and rapid-cycling BD. Particular attention has been paid to the results of the randomized clinical trials. Case studies and the results of uncontrolled clinical reports have been used only on an exceptional basis. The way in which the review was conducted differs however to a certain extent from chapter to chapter and a description of the methods of review is therefore provided in the preface to each chapter.

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2. Treatment of acute mania

by E. Timuçin Oral

2. 1. Introduction

The DSM-IV criteria for mania require: a distinct period that represents a break from pre-morbid functioning, a duration of at least one week, elevated or irritable mood, at least three to four classical manic signs and symptoms and the absence of any physical factors. Although not specifically mentioned in the ICD-10 or the DSM-IV definitions, delusional, hallucinatory, even first-rank, psychotic experiences can occur in mania (Hirschfeld et al, 2003). Acute mania can be subdivided into classical pure mania, mania with mood-congruent or mood-incongruent psychosis, mixed state and rapid-cycling mania. One quarter to two thirds of all manic episodes are associated with delusions, while 13% to 40% are associated with hallucinations. Mixed episode is a complex syndrome which is difficult to diagnose, has the most prolonged duration of bipolar episodes and more frequent psychotic profile than pure mania with high suicidality and poor response to drugs. Mixed state mania has been well known since Krapelin and listed in classification systems with criteria that include both a manic and a major depressive episode nearly every day for at least a one-week period. On the other hand, mixed-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electro-convulsive therapy or light therapy) should not contribute toward a diagnosis of Bipolar I Disorder (Goodwin & Jamison, 1990). Although, theoretically, mania is supposed to be resolved within 1–3 months even without treatment, psychiatric hospitalization is very common in especially severe cases due to functional impairment. Current treatments for mania aim to control the agitation, impulsivity, aggression and psychotic symptoms and to help patients regain their pre-morbid functionality. However, the clinical management of mania is challenging as most patients show

syndromal remission but incomplete functional recovery after the first episode of mania (Tohen et al, 2000).

Practice guidelines recommending treatment strategies are widely available in every country and there is also a trend toward evidence-based medicine. Thus, treatment guidelines should be both evidence-based and flexible enough to meet the needs of individual patients. Recent treatment strategies have mostly recommend lithium, valproate or an antipsychotic as a first-line monotherapy, and combinations of the same agents as second-line treatments. The mania treatment algorithm of the Expert Consensus Guidelines (Sachs et al, 2000) divides patients into four classes: euphoric, mixed/dysphoric, psychotic and rapid cycling. Valproate is the drug of choice for mixed mania and rapid cycling, while either valproate or lithium is the first choice for euphoric mania. For psychotic mania, the guidelines recommend valproate or lithium plus an antipsychotic. Practice guidelines released by the American Psychiatric Association (2002), the British Association for Psychopharmacology (Goodwin, 2003) and the World Federation of Societies of Biological Psychiatry (WFSBP) (Grunze et al, 2003) are all evidence based.

It is common practice to administer conventional antipsychotics to treat acute mania (Zarate and Tohen 2000) despite well-known extrapyramidal side effects. It is estimated that antipsychotics are prescribed to over 90% of patients with acute mania, either in combination or as a monotherapy (Chou et al, 1996; Tohen et al, 2001). The novel antipsychotics have several advantages over the conventional "neuroleptics" and they have been increasingly used in bipolar mania, mostly because of their more favorable side effect profiles. A clinically important consideration is whether novel antipsychotics may be more or less effective in particular subtypes of mania, analogous to the finding that lithium may be more effective in pure mania than in mixed states. Second generation antipsychotics have been administered to treat mania in three aspects: 1) to treat psychotic symptoms 2) to control agitation (some new drugs like olanzapine and ziprasidone have intramuscular preparations which may increase their use for agitation) and 3) they may have a specific anti-manic effect (Breier et al, 2002). Double-blind monotherapy (and add-on) studies have indicated the effectiveness of olanzapine, risperidone, quetiapine, ziprasidone and aripiprazole in the treatment of mania.