The need for cost-effective choices to treat patients with bipolar 1 disorders including asenapine.

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Abstract

Bipolar 1 disorders (BPD) are a chronic disorder with prevalence rates up to 2.6% of the adult population or higher and appreciable direct and indirect costs. As a result, a concern to health authorities especially given the low age of onset. Consequently, a need to treat BPD patients well and improve their quality of life. Pharmacotherapy includes mood stabilisers and atypical antipsychotics (AAPs). AAPs have different mechanisms of action and side-effects so treatment needs to be tailored. Asenapine in clinical trials is as effective as olanzapine with less metabolic side-effects. Chitnis and colleagues have shown in routine care that asenapine also reduces hospital and emergency room admissions making it cost neutral in BPD, which is of interest to health authorities and clinicians.

Main Text

Bipolar I disorders (BPD) are a chronic disorder involving one or more episodes of mania or mixed mood, associated with increased psychomotor activity, excessive social extroversion, decreased need for sleep, impulsivity, impairment in judgment, and grandiose mood. Patients may also experience delusions, paranoid thinking, and extreme agitation (1, 2). Published prevalence rates vary from 0.4 to 1.6 percent up to 2.6% of the adult population (1, 3) or higher, especially if the impact of under-diagnosis and misdiagnosis are included (2, 4, 5). As Chitnis and colleagues point out, in view of the high prevalence of BPD including both psychiatric and associated medical conditions including thyroid disease, migraine, heart disease and diabetes, overall expenditure on this condition is high (3). Direct medical costs were calculated at over US$30.7billion per year in the US alone in 2009, with indirect costs greater than US$120billion annually (2, 3).

This high prevalence and costs associated with BPD are a concern to health authorities and health insurance companies world-wide as they struggle with increasing pressures due to ageing populations and the continued launch of new high priced medicines (6, 7). Concerns are increased by the low median age of symptom onset at just 20 to 25 years of age (1, 3). Consequently, there is a recognised need to treat these patients well to improve their quality of life and reduce emergency room visits and in-patient care.

Pharmacologic treatments for BPD include mood stabilizers, e.g. lithium, valproate, lamotrigine, and carbamazepine, as well as atypical antipsychotics (2). The American Psychiatric Association and others recommend polytherapy, e.g. lithium or valproate in conjunction with an antipsychotic, for patients with severe manic or mixed episodes and monotherapy, e.g. lithium, valproate, or an antipsychotic, for less ill patients with atypical antipsychotics (AAPs) preferred to typical antipsychotics because of their improved side-effect profile (1, 8-10). However other authors have questioned the distinction between first generation (typical) and second generation (atypical) antipsychotics as there are different domains of effectiveness and safety between the different antipsychotics (11). For instance, the extent of extrapyramidal side-effects seen with haloperidol depends on the doses prescribed (11).

Never-the-less, it is recognised by all healthcare professionals that the different AAPs have different mechanisms of action and different effectiveness and safety profiles in patients with major mental illness including BPD (1, 11-14). Consequently, the choice of AAP prescribed should be tailored to the individual, especially as there are concerns with the effectiveness of some of the current AAPs for the management of depressive phases of bipolar disorders (10, 13). This does not include asenapine, which in short-term trials has demonstrated significant superiority to placebo in treating the manic symptoms of BPD and, in longer term studies, showed comparable efficacy with olanzapine in treating

manic and depressive symptoms of BPD with less impact than olanzapine on adversely affecting triglycerides, weight and cholesterol levels (15, 16). As a result, post-hoc analysis of two short-term clinical trials demonstrated asenapine as a cost-effective alternative to olanzapine in mixed episode BD-I patients, and may have specific advantages in this population, potentially leading to healthcare savings and improved outcomes (17).

However healthcare professionals, especially budget holders, prefer to see the effectiveness, safety and costs of medicines in routine clinical care to aid decision making rather than clinical trials as there can be appreciable differences in patients enrolled into clinical studies versus those seen in routine clinical care, i.e. real life. As a result affecting the generalisability of the findings from clinical trials (7). This is because Phase III clinical trials are typically conducted under ideal and highly controlled conditions to seek high internal validity to maximise the chance of demonstrating clinical benefit (7). Consequently, patients in routine clinical practice may in fact be more elderly and have greater co-morbidities than those seen in clinical trials.

This is the strength of the paper by Chitnis and colleagues (3). The authors assessed the impact of asenapine in new users, who are part of two large healthcare claims databases in the US, on subsequent utilisation and health care costs (3). The size of the combined databases, including both commercially insured personnel and Medicare enrolees, is appreciably larger than the total number of patients in most European countries at approximately 30 million. In view of this, providing an appreciable number of patients (1403) meeting the strict entry criteria, which excluded for instance patients with evidence of any use of depot antipsychotics during pre- or post-index as this may indicate patients who have difficulties complying with oral regimes (3). As a result, providing robustness to the findings.

Robustness in the assessment of health care resource utilisation and costs is further facilitated by the comprehensive datasets used and the rigorous validation process. Datasets include detailed in- and out-patient medical claims data, incorporating both diagnoses and procedures, provider types, place of service and total reimbursed costs (3). Pharmacy claims included all medication dispensed and their details including reimbursed amounts.

Encouragingly the authors found that healthcare resources decreased following asenapine. Hospital admissions, emergency room visits, outpatient hospital visits and physicians' office visits were all down (all $p<0.05$) (3). In addition, the findings were similar among patients with and without evidence of AAPs during the pre-index period. Whilst pharmacy costs increased by on average by US$839 per person during the post-index period, this was offset by a corresponding reduction of US$1806 in the cost of in-patient care, leading to an overall decrease in total BPD related costs of US$979. These are total costs lower rather than marginal costs in view of the methodology employed. However, these costs do not include indirect costs, which are substantial for this patient population (2, 3).

Whilst the median age of patients with BPD in this dataset was higher at approximately 44 years compared with published studies of at 20 to 25 years of age (1, 3), the authors satisfactorily explain this difference. This included the fact that it can take up to 10 years from the time of symptom onset to reach a definitive diagnosis of BPD, and atypical antipsychotics may be reserved until other therapies such as mood stabilisers are found to be ineffective or intolerable (3).

Overall these findings give confidence to all healthcare professionals that asenapine is an effective AAP for this group of patients, reducing inpatient services and emergency room visits, potentially enabling patients to function well enough to benefit from other psychosocial therapies. As mentioned earlier, this meets the goal of health authorities in this area of unmet need. Whilst health authorities typically do not get involved with directing the choice of AAP prescribed in view of the complex issues with managing this population and the need to individualise treatment apart from potentially looking at different dosage forms (6, 18, 19), despite suggestions to the contrary (13), they should be reassured by these findings. This is different to the situation where there can be concerns with bias in the study findings as seen with for instance with long-acting injectable AAPs where a number of the published studies are open label and subject to significant selection and sponsor bias (20).

We look forward to longer term follow-up of patients prescribed asenapine to give further confidence to all healthcare professionals involved with the management of patients with BPD.

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