

Current Debates on Determining most Cost Effective Treatment for Psychosis and Bipolar I Manic / Mixed States

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Inclusion of second-generation antipsychotics (SGAs) into psychiatric armamentarium has changed not only the quality of life and functioning of patients with severe psychiatric disorders but also public and professional perception of such disorders and antipsychotic drugs. Most unpleasant adverse effects experienced with first-generation antipsychotic drugs (FGAs) for example, depressed mood, cognitive impairment, extrapyramidal side effects, tardive dyskinesia, endocrine and cardiac risks were either absent or minimally present with SGAs (1,2). These positive perceptions on the measures of safety and tolerability as well as accumulation of efficacy data on psychotic disorders and bipolar manic / mixed states along with hard-to-treat depressive episodes increased prescription of SGAs substantially. Consequently, nowadays more antipsychotic drugs are being prescribed on a broader range of psychiatric conditions compared to past (3–5). Roughly, more than three quarters of the prescribed antipsychotics are SGAs and average cost of a SGA is roughly 10–50 times more than a classical antipsychotic (5, 6). These observations and facts on top of global financial difficulties prompted health care systems internationally to search for justifications for use of cheaper treatment alternatives and more cost effective employment of expensive ones (6). As such several recent meta-analyses assessed efficacy, safety, and tolerability of SGAs over FGAs and/or other medications for treatment of psychosis and bipolar manic / mixed states (5–8).

A large meta-analysis involving 114 studies compared efficacy and safety of SGAs versus FGAs in treatment of schizophrenia or related psychosis (6). Broad inclusion criteria allowed blind and open, randomized and non-randomized controlled trials with study durations ranging from less than 1 day to 4 years as well as retrospective cohort studies with study durations ranging from 3 to 22 years (6). More than half of the included studies was multi-centered (54%) and supported by pharmaceutical industry (68%). In terms of efficacy moderate strength evidence showed a benefit for risperidone compared with haloperidol on the Positive and Negative Syndrome Scale (PANSS); difference was not considered clinically important.

Moderate strength evidence also showed clinically important benefit of haloperidol over olanzapine on the Scale for the Assessment of Positive Symptoms (6). Moderate strength evidence showed clinically important benefit of olanzapine over haloperidol on the PANSS, Scale for the Assessment of Negative Symptoms, and Montgomery-Asberg Depression Rating Scale with no indication of publication bias (6). Moderate strength evidence showed clinically important benefit for clozapine compared with chlorpromazine based on the total score from the Brief Psychiatric Rating Scale. Results for functional outcomes were available for only 9 studies on different comparisons. For the 4 key adverse events (diabetes mellitus, death, tardive dyskinesia, or a major metabolic syndrome) the strength of evidence was insufficient to draw conclusions for most comparisons (6). Two trials each provided data on mortality of for chlorpromazine vs clozapine, and haloperidol vs aripiprazole with minor absolute rate differences. For the latter comparison the study duration was only 24 hours (6). Low strength evidence showed a higher incidence of the metabolic syndrome for olanzapine than for haloperidol in 2 relevant studies; and tardive dyskinesia for chlorpromazine than for clozapine; risk differences were 5% and 9% at 12 weeks and 9 years (6).

Over a more homogenous data set including 150 double-blind, mostly short-term studies, with 21,533 participants with schizophrenia, Leucht et al. (2009) compared nine SGAs with FGAs for overall efficacy, positive, negative and depressive symptoms, relapse, quality of life, extrapyramidal side-effects, weight gain, and sedation (5). They reported superior overall efficacy, for amisulpride, clozapine, olanzapine, and risperidone in comparison to FGAs. The other SGAs were not more efficacious than the FGAs, even for negative symptoms (5). SGAs induced fewer extrapyramidal side-effects than did haloperidol (even at low doses). With the exception of aripiprazole and ziprasidone, SGAs induced more weight gain, in various degrees, than did haloperidol but not than low-potency FGAs. The authors concluded that SGAs differ in many properties and are not a homogeneous class and recommended for individualized

treatment based on efficacy, side-effects, and cost (5).

Recent meta-analysis of antipsychotic drugs for treatment of bipolar mania indicated superiority over placebo for aripiprazole, asenapine, cariprazine, haloperidol, olanzapine, paliperdone, quetiapine, risperidone, and ziprasidone (7-9). In regard to comparative efficacy and safety assessment of antimanic drugs paucity of head-to-head trial data prompted use Bayesian approach for multiple treatments meta-analysis (MTM) approach for bipolar mania (10-12). Two recent applications of the technique one with inclusion of monotherapy trials only, indicated larger effect sizes for carbamazepine (Standardized mean difference-SMD= +0.20), risperidone (+0.16), valproate (+0.14), ziprasidone (+0.13), olanzapine (+0.10), asenapine (+0.08), and smaller effect size for haloperidol (-0.04) compared to the MTM including both single-agent as well as add-on trials (8, 9). The network over single-agent antimanic treatment trials indicated superior short-term efficacy of olanzapine over asenapine, lithium and valproate; of risperidone over valproate and ziprasidone; and of carbamazepine over valproate (8,9). No meta-analytic assessment of clinically important short-term or long-term adverse effects of antimanic treatments is available. However, the MTM including both single-agent as well as add-on trials by Cipriani et al. (2011) compared all cause drop-outs among those anti-manic treatments and reported better short-term tolerability of olanzapine, risperidone, and quetiapine (9). Since early drop-outs may also result from inefficacy how much that data reflects acceptability of given treatment is questionable. More importantly, recent meta-regression findings on factors associated with placebo responses reflect how the patient characteristics and trial sets of acute mania studies were different (13). That report raise concerns on a valid application of MTM approach for evidence synthesis over acute mania studies (8).

In conclusion, these meta-analyses can not provide a reliable evidence synthesis on treatment-induced adverse effects of SGAs vs FGAs (5,6,9). Yet, scarce data may indicate better safety profiles for at least certain SGAs compared to FGAs (5,6,9). Quantifiable clinical data on short- as well as long-term assessments of SGAs

vs FGAs on the measures of treatment induced mood switches, cognitive functions, extrapyramidal side effects, tardive dyskinesia, endocrinological, metabolic, and cardiac risks are most needed. Application of MTM techniques on such data along with data on efficacy and cost may potentially provide most meaningful comparative cost-effectiveness (CE) analysis. Consideration of quantifiable measures of neuronal viability or neuroprotection as reflected by molecular or imaging data on neurotrophic factors or brain' N-acetyl aspartate levels associated with use of such psychotropic drugs once available would crown such a decision-analytic CE model. It is noteworthy in that sense that accumulated evidence indicates accelerated neuronal and glial loss in bipolar patients and reversal of such loss by optimum use of lithium and valproate (14-15). More to the point, there is preclinical data indicating haloperidol induced decreases in whole brain volume and cortical gray matter as compared to lithium, which by contrast increased both (16). Limited preclinical evidence also indicates some neuroprotective effects by use of olanzapine and risperidone (17-20). Such effects of antipsychotics or mood stabilizers on protection of neuroresilience may reflect clinically on patient's higher executive functions and cognition (21).

Considering these factors, for example, a decision-analytic model including data on efficacy and cost might credit haloperidol as the cheapest effective antipsychotic or antimanic treatment, while data on patients' functionality, quality of life, and total life- as well as working- years gained might favor lithium or a SGA. While having potentially better efficacy and short-term tolerability profile, olanzapine might get a lower total score owing to its long-term metabolic effects. Therefore, if a decision-analytic CE model is to be developed for psychosis or bipolar mania in addition to apparent ranking of drugs by efficacy and cost, such a CE model should include quantifiable data on full clinical recovery, functional status, cognition, neuroprotection, switch to depression and risk of suicide as well as adverse metabolic and neurologic effects as they become available.

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