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Review Article

An algorithm for pharmacological treatment of mania during hospitalisation

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ABSTRACT

Current evidence for pharmacological treatment of mania during hospitalisation is insufficient as there are no larger well-designed randomised trials of comparative medical treatments of mania during inpatient stays. Moreover, there is considerable variation in pharmacological medication in clinical practice during hospitalisation for mania. Based on a hospital data overview, a systematic search of the literature and a three-day consensus meeting, this narrative review proposed an algorithm for optimised pharmacological treatment of mania during hospitalisation and its subsequent scientific evaluation.

KEY POINTS

- A combination of olanzapine and lithium should be provided in antimanic doses from treatment initiation.
- Quetiapine should be used in case the patient does not tolerate olanzapine.
- ECT is first-choice treatment in severe agitated and psychotic mania, manic delirium or in case of prior non-response to drug treatment.
- Aim: substantial improvement of sleep and activity (≤ 2 on the Young Mania Rating Scale) after five days.

Within psychiatry, like in other areas of medicine, randomised controlled trials (RCTs) represent the gold standard for obtaining information on how treatment affects health [1]. In relation to mania, a new systematic review and random-effects model network meta-analysis identified 72 double-blind placebo-controlled RCTs of 23 drugs, showing that antipsychotics, carbamazepine, lithium, tamoxifen and valproate were superior to placebo in terms of response for acute mania although only aripiprazole, olanzapine, quetiapine and risperidone had a lower all-cause discontinuation than placebo [2]. Achieving results from RCTs with high internal and external validity [1] is a major challenge within psychiatry because of the nature of psychiatric illnesses, including mania [3, 4]. The complex and labile symptomatic presentations, a tendency for patients to deny illness and reject treatment, and diagnostic heterogeneity severely complicate the design and conduct of experimental treatment trials in bipolar disorder [5]. In this way, most real-life patients with bipolar disorder are excluded due to several factors including psychotic symptoms, comorbidity, severity, suicide risk and poor illness insight, cooperation and adherence to medication [5, 6]. It is estimated that as few as one in ten patients with bipolar disorder presenting as potential research subjects will be recruited into a long-term trial involving a placebo condition [5]. For these reasons, it is unsurprising that only few RCTs exist on placebo controlled or comparative treatment of different drugs for mania during psychiatric hospitalisation when patients are severely ill, with decreased illness insight and willingness to accept treatment.

This narrative review aims to propose a pragmatic clinical algorithm for optimised pharmacological treatment of mania during hospitalisation that goes beyond the incomplete evidence from RCTs.

METHODS

The narrative review follows a “state-of-the art” approach for selected topics [7] aiming to “address more current matters” and “offer new perspectives on an issue or highlight an area in need for further research”. The review integrated four scientific parts:

I An overview of data on the use of medication, electroconvulsive therapy (ECT) and coercion in patients hospitalised for mania from the Mental Health Services, Capital Region of Denmark.

II A systematic literature search conducted on Pubmed, Embase and Psychlit on RCTs on comparative pharmacological treatment for inpatient mania.

III A three-day consensus meeting (in Danish: “Forbedringsevent”) on “Optimised treatment for inpatient mania” to process improvements that deliver quality and productivity results in organisational settings [8, 9]. For three days, 37 researchers, clinicians and patients participated in the meeting to achieve and describe, based on structured presentations and questions, consensus on an algorithm for “Optimised treatment of mania during hospitalisation” that goes beyond current evidence. The participants of the meeting and the authors of the present article have 10-30 years of experience with research into and diagnostics and treatment of bipolar disorder,

including treatment of mania during hospitalisation.

IV A description of a subsequent scientific evaluation of the effects of the algorithm "Optimised treatment for inpatient mania".

RESULTS

The results of the four scientific parts are described below:

I Overview of data from the Mental Health Services, Capital Region of Denmark

The Mental Health Services, Capital Region of Denmark, cover a population of 1.8 million inhabitants (2019). Data extracted for the present study from the Mental Health Services, Capital Region of Denmark, include all 2,216 patients hospitalised with a diagnosis of a single manic episode (ICD F30) or bipolar affective disorder, currently mania (ICD10 F31.1-F31.21), from 1 March 2020 to 28 February 2021. The data revealed significant unexplained differences between the centres in the use of medication (lithium, antipsychotics, anticonvulsants and antidepressants), ECT and coercion both overall for patients with a diagnosis of bipolar disorder and within the various states of bipolar disorder (mania/bipolar depression/mixed state. Details are available from the first author).

II The systematic literature search and international guidelines

The systematic search on Pubmed, Embase and PsychLIT (1 September 2022, replicated 5 June 2023. Search terms: Mania AND randomised AND (inpatient OR hospitalised) AND pharmacological treatment) returned 501 separate articles among which only two compared different drugs for inpatients: An initial small RCT of severely ill hospitalised patients with mania showed that lithium carbonate or haloperidol improved manic symptoms compared with chlorpromazine [10]. A more recent three-week RCT found a similar response to olanzapine as to risperidone for inpatients with mania but greater improvements in secondary measures of severity and depressive symptoms and more weight gain [11]. Overall, it is evident that RCTs in mania offer little direction for the clinician in terms of specific suggestions for preferred drug or drug combinations, as also reflected in international guidelines on mania [12-16]. As summarised in the 2018 guideline from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) 2018, lithium, divalproex, aripiprazole, paliperidone, risperidone, asenapine, olanzapine, quetiapine and cariprazine are all recommended as first-line treatment options with level 1 comparable efficacy evidence (Cohen's d: 0.32-0.66; small to medium effect size). However, only around 50% of manic patients will respond to monotherapy within 3-4 weeks according to clinical trials [15]. In short, the individual clinician may obtain only limited guidance from RCTs and is left with many choices.

III Algorithm prepared following the three-day consensus meeting on "Optimised treatment for inpatient mania"

We recommend that treatment is initiated as soon as the diagnosis of primary manic episode is made, i.e. when organic cause or alcohol or substance abuse is excluded. If the patient is known as an outpatient, this should be clarified (if possible) prior to admission.

Initial target for inpatient treatment of mania

The aim of the treatment is to reduce the severity of the manic episode after five days of hospitalisation (day 5), defined as improvement of two central measures of mania, sleep and activity (score ≤ 2), on the Young Mania Rating Scale [17]. ECT is considered first-choice treatment, especially in severe agitated and psychotic mania, manic delirium and in case of prior experience with insufficient effect of pharmacological treatment.

Basic treatment from day 0: olanzapine and lithium

A combination therapy of olanzapine and lithium is initiated from day 0:

1. Olanzapine: 15 mg at 10 p.m. day 0. In case of lack of effect at day 1: 10 mg (morning) + 20 mg (at 10 p.m./bedtime). Dosed up to 40 mg. If injection is required, up to 10 mg × 2 intramuscular may be given.

If the patient does not tolerate olanzapine:

Peroral quetiapine immediate release (IR) is initiated with 100 mg daily, increasing to 400-800 mg quetiapine extended release (XR) and then to a maximum dose of 1,200 mg daily, depending on effect and side effects.

If injection is required, aripiprazole 9.75 mg may be used intra-muscularly, a maximum three times daily with a minimum two-hour interval between each injection.

2. The antimanic effect of lithium occurs a few days later than the effects of antipsychotics. Before initiating treatment, kidney and thyroid function tests and electrocardiogram are performed. The plasma concentration should be around 1.0-1.2 mmol/l according to frequent measures. Lithium treatment should be initiated concurrently with the antipsychotic treatment, partly as supplementary antimanic treatment, partly as initiation of prophylactic treatment.

3. If necessary, supplement with tablet lorazepam 4 mg in the evening of the first day, increasing to a maximum dose of 10-12 mg/24 hrs if necessary to achieve the treatment goal. Alternatively, lorazepam 2-4 mg may be injected intra-muscularly (same recommended maximum dose).

Day 5

4. If treatment with the above-mentioned points 1-3 has not reduced the severity of the manic episode after five days, the decision is made for either valproate as augmenting therapy (note contraindicated for fertile women, and normal liver tests are required) or ECT [18].

A plan must be prepared for completion of the antimanic treatment. Tapering off first the benzodiazepine and then the antipsychotic should be achieved in weeks or months, ensuring that

sufficient and preferably somewhat prolonged sleep is maintained throughout the tapering period.

Background for the algorithm

Combination of olanzapine and lithium from day 0:

Monotherapy is recommended as first-line treatment for acute mania in most guidelines [12-16], but substantial variability characterises the efficacy of the different drugs used, although some provide more homogenous and predictable improvements of manic symptoms [19]. Furthermore, augmentation trials of a mood stabiliser and an antipsychotic show greater mania improvements than monotherapy studies, especially in patients with greater severity [20]. Thus, initial combination therapy from mania treatment initiation is more efficacious than second-generation antipsychotic monotherapy [21, 22].

As recently highlighted [23], olanzapine in mono- or polytherapy is estimated to provide level 1 efficacy in acute mania and is recommended as a first-line treatment for acute mania in several guidelines [12, 24, 25]. However, other guidelines consider it a second-line treatment because of its long-term tolerability and metabolic issues [15, 26, 27]. It is key to consider that in the acute phase of mania, especially with severe symptoms, the anxiolytic properties of olanzapine can be very useful in reducing anxious distress during the first weeks of an acute episode [23]. Furthermore, it is a clinical experience that olanzapine has a rapid onset and sedative effect and is easy to dose. Finally, olanzapine can be administered as intramuscular injections. In light of these observations, we recommend olanzapine as a first-line antipsychotic, keeping in mind that its use should be transitory and goal-directed, avoiding long-term treatment.

Quetiapine as a second-line antipsychotic

For non-hospitalised patients, quetiapine probably has the same antimanic effect as olanzapine while also providing a convincing effect in bipolar depression and in preventing the development of bipolar depression [15].

Aripiprazole may be used in patients in whom risks of metabolic side effects are estimated to be heightened. If aripiprazole is chosen, a higher need for benzodiazepines than with olanzapine/quetiapine must be expected.

The efficacy of lithium in antimanic doses and valproate is well documented in mania for non-hospitalised patient populations as is the effect of ECT in hospitalised patients with mania [15]. The treatment is part of treatment practice in large parts of the world and good experience is common with the effect of both olanzapine, lithium, valproate and ECT during hospitalisation.

ECT in primary mania during hospitalisation

Based on data from seven RCTs, it was concluded that ECT is an effective treatment for mania with high remission rates and rapid onset of effect, and that ECT may be more effective than lithium monotherapy and antipsychotic medication [28]. ECT is specifically indicated in severe agitated

and psychotic mania due to the increased risks of developing delirium [28]. It is recommended that patients continue prophylactic treatment with lithium during ECT as lithium prevents the development of depressive relapse after ECT [29] and with a plasma lithium level of approx. 0.6-0.7 mmol/l to reduce the risk of inducing delirium [30].

Finally, as highlighted in the in the 2018 guideline from the CANMAT and ISBD guideline, treatment choices for the individual patient may further be guided by clinical feature specifiers, such as prior course of illness, the current symptomatology of the manic episode and safety/tolerability issues [15].

Discharge from psychiatric hospital

Patients often develop depression after hospitalisation with mania even on combination treatment with lithium and olanzapine. A decision must be made regarding the continued medication, specifically the possible switch/crossover from olanzapin to quetiapin in the outpatient setting to prevent or treat a post-manic depression [15]. If the patient is not shifted to quetiapine, a decision must be made to gradually taper olanzapine. During and after hospitalisation, parameters related to the risk of developing metabolic syndrome during treatment with antipsychotics must be monitored systematically (weight, waist measurement, triglycerides and lipids, etc.).

IV Scientific studies on optimised treatment of mania during hospitalisation

We are currently investigating the effect of the proposed “Optimised treatment of mania during hospitalisation” algorithm in two different ways – as part of the Clinical Academic Group (CAG) Bipolar randomised one-year trial [31] and in a combined observational and qualitative study of patients hospitalised with mania. As part of the CAG Bipolar RCT, patients with bipolar disorder in Psychiatric Centre Copenhagen, who are randomised to active specialised CAG Bipolar outpatient treatment in the CAG Bipolar RCT, are admitted to a selected acute intensive care unit (A1) and to four selected affective wards. Conversely, patients randomised to general outpatient care are hospitalised, if needed, to control units correspondingly consisting of another acute intensive unit (A2) and other hospital wards in Psychiatric Centre Copenhagen. For the two intervention groups, the following one-year outcome measures are estimated based on register data: 1) number and cumulated durations of hospitalisations and 2) use of medication, ECT and coercion during hospitalisation.

DISCUSSION

This narrative review proposed an algorithm for "Optimised treatment of mania during hospitalisation".

Limitations

An inherent limitation of the "Optimised treatment of mania during hospitalisation" algorithm is that it is not entirely based on the results from randomised trials and, specifically, that no RCT was

conducted on the effect of initial combined olanzapine and lithium versus sequential treatment.

Advantages

The narrative review and proposed algorithm comprise a synthesis of an overview of hospital data from the Mental Health Services, Capital Region of Denmark; a systematic literature search including international guidelines; the authors' more than 10-30 years of experience with research, diagnosing and treatment of bipolar disorder and a three-day consensus meeting among the authors [8, 9], including 37 researchers, clinicians and clinical managers and with patient participation. Furthermore, it is a strength that the effect of the algorithm is investigated in a pragmatic RCT, and future implementation of the algorithm will depend on these results. Moreover, it is a strength of the algorithm that a recently published recommendation from Barcelona also proposes initial first-line combination treatment with lithium and olanzapine for severe mania or, alternatively, quetiapine and second-line treatment with valproate or ECT [23]. Finally, in line with the present paper, the Barcelona paper recommends that “previously diagnosed bipolar disorder patients should commence antimanic agents without delay”, i.e. from day 0 in case of hospitalisation [23].

CONCLUSION

The present narrative review proposed for the first time an algorithm of optimised pharmacological treatment of patients hospitalised with mania. The algorithm goes beyond the scientific evidence as no well-designed randomised trials exist comparing different drug treatments or combinations of treatment of mania during hospitalisation. Other choices and recommendations could have been made, and therefore it is an advantage of the present Copenhagen algorithm that the effect of the "Optimised treatment of mania during hospitalisation" is scientifically evaluated in the CAG Bipolar RCT [31] and in a qualitative and observational study of therapists' and patients' experiences during hospitalisation.

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