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Reply to "Algorithm or not for pharmacological treatment of mania during hospitalisation"

Licht et al. advocate for the traditional sequential treatment of inpatient mania with an antipsychotic and, if necessary, an adjunctive benzodiazepine, and, in select cases, with valproate and potentially lithium at a later stage, arguing for "a nuanced approach to treatment algorithms that prioritises patient-centred care" [1]. Such an approach may be fruitful for clinical experts in bipolar disorder but leaves younger and less experienced clinicians with complex and, in many cases, unclear choices. Thus, a total of nine drugs 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) by the 2018 guideline from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorders (ISBD) 2018. These nine drugs are lithium, divalproex, aripiprazole, paliperidone, risperidone, asenapine, olanzapine, quetiapine and cariprazine [2]. Conversely, it is well known from clinical trials that only approx. 50% of manic patients will respond to monotherapy within 3-4 weeks [2]. In short, the individual clinician is poorly guided by RCTs and is left with a range of difficult choices.

The proposed algorithm for treatment of patients hospitalised for mania is based on 1) an overview of data showing considerable and unexplained differences between the centres of the Mental Health Services in the Capital Region of Denmark concerning use of medication, electroconvulsive therapy (ECT) and coercion, 2) a systematic literature search and 3) a three-day consensus meeting attended by 37 researchers, clinicians and patients with extensive experience with inpatient mania, aiming to propose an optimised treatment algorithm for inpatient mania [3].

The Copenhagen algorithm for pharmacological treatment of mania during hospitalisation is in line with the recommendations of another internationally leading centre, the Barcelona Group, which also proposes initial first-line combination treatment with lithium and olanzapine for severe mania or, alternatively, quetiapine and second-line treatment with ECT or valproate [4]. As highlighted by the authors [4], combination therapy has shown greater efficacy than mood stabiliser monotherapy (such as lithium), with 20% more patients responding, especially in more severely affected patients. Furthermore, combination therapy was suggested to be more efficacious than second-generation antipsychotic (SGA) monotherapy. In line with our group, the Barcelona Group also recommends that "previously diagnosed bipolar disorder patients should

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commence antimanic agents without delay", i.e. from day 0 in case of hospitalisation [4].

Patients who are hospitalised for mania often endure an exhausting course characterised by a "trial and error" approach with recurrent drug trials frequently resulting in pre-delirium and, ultimately, delirium states. Treating inpatient mania is inherently challenging. We believe that the proposed algorithm will aid the general clinician and potentially improve and shorten inpatients' stays for mania. We recognise the limitations of designing an algorithm for inpatient treatment but have prioritised recommendations for efficient treatment of severe mania. We are currently testing the implementation and effects of the Copenhagen algorithm for pharmacological treatment of mania during hospitalisation in a sub-study of the ongoing Clinical Academic Group (CAG) Bipolar randomised trial [5] concerning durations of hospitalisations and use of medication, ECT and coercion, and will revise it accordingly.

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