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SCIENTIFIC LETTER

Treatment of acute mania with methylphenidate: Therapeutic approach based on a new pathophysiological model☆

Tratamiento de la manía aguda con metilfenidato: propuesta terapéutica basada en un nuevo modelo fisiopatológico

Dear Sir:

The initial treatment for patients with acute mania represents a significant clinical challenge, given that treatments for mania symptom control usually take several days to start acting. Most treatments available for the manic phase of bipolar disorder are sedatives, to lower the hyperactivity and excitation that patients with mania present. However, recent observations[1] indicate that these symptoms may be the result of a self-regulating mechanism consisting of an increase in excitation and activity to compensate a deficit in vigilance or arousal. What is involved is a physiopathological model that proposes the existence of a state of brain hypoactivation in mania and that can open new therapeutic approaches.

The arousal regulation model has recently been proposed as a physiopathological mechanism that may be altered in affective disorders. The transition from the arousal state to that of sleep corresponds to different neurophysiological levels of vigilance, so various brain activity stages can be measured using electroencephalography (EEG). Regulating arousal levels implies an adaptive physiological mechanism that can adapt to an individual's biological needs and to environmental circumstances. For example, in situations of danger the organism raises the arousal level to face the situation, while vigilance drops in rest periods. In addition, continued states of increased arousal are often linked with the tendency to withdraw from external stimulation; in contrast, tired states can be associated with hyperactive behaviour as a self-regulating attempt to maintain arousal level. Based on this model, some vulnerable individuals present alterations in the self-regulating physiological arousal mechanisms, so states of brain hypoactivation or lowered arousal levels might lead to a clinical picture of mania. This unstable arousal regulation can have a pathogenic role in mania. Sleep deficits and other factors that destabilise arousal set off a self-regulating behavioural syndrome characterised by hyperactivity and increased speech and distractibility. In vulnerable individuals, the self-regulating mechanism could cancel out the physiological tendency to seek sleep, which can aggravate sleep deficits and increase instability in arousal regulation. In turn, this would trigger a vicious circle causing full-blown mania. This pathogenic concept provides an explanation for various aspects that are apparently paradoxical. First of all, in contrast to clinical observation of hyperactivity, evidence based on EEG data shows that patients with mania rapidly move towards low arousal level, frequently in the first seconds of the EEG record.[2] Secondly, the sleep deficit or life experiences that alter sleep-arousal regulation can trigger or worsen manic behaviour.[3] Finally, suspending substances that stabilise arousal (such as nicotine) can precipitate manic episodes.[4]

All these data suggest that psychostimulant drugs can be useful in treating some clinical conditions of mania. Likewise, observation of patients with attention deficit hyperactivity disorder (ADHD), a disorder with high comorbidity and wide overlaps in symptoms with bipolar disorder,[5] also provides arguments in favour of using psychostimulants to treat mania: these drugs reduce attention deficits, sensation-seeking behaviour and hyperactivity in patients with ADHD[6]; methylphenidate improves sleep in children and adults with ADHD; psychostimulants in children with ADHD and additional manic symptoms are effective in reducing both the symptoms of ADHD itself and the manic symptoms.[7]

In addition, the efficacy of psychostimulants in the initial treatment of acute mania has been confirmed: in some isolated cases, manic symptoms have improved rapidly and clearly after administering these drugs in adult manic patients with bipolar disorder.[2,8,9] A recent study[10] demonstrated the efficacy of a psychostimulant, modafinil, in mania symptoms. In addition, this clinical improvement was associated with a stabilisation of vigilance.

Although psychostimulants have sometimes been associated with inducing mania,[11] the turn to mania seldom occurs. Some studies[12,13] on children with bipolar disorder and ADHD found that using psychostimulants added to the treatment with a mood stabiliser not only improved the ADHD symptoms, it also improved those of mania. Furthermore, a systematic analysis performed by the US Food and Drug Administration[14] found low frequency of

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symptoms similar to mania in patients with ADHD treated with methylphenidate. Consequently, the risk of worsening mania seems low.

Using psychostimulants to control mania symptoms in bipolar disorder is a novel therapeutic approach with a physiopathological basis in the model of unstable vigilance regulation in affective disorders. To test the usefulness of this therapeutic proposal, which would mean a significant change in focus for bipolar disorder treatment, clinical assays with psychostimulants during mania stages are needed. The fact that methylphenidate acts very rapidly can facilitate early control of the symptoms of acute mania, which would be an advantage compared with other types of treatment currently available. We have now initiated an international multicentre clinical assay with academic institutions in Germany, Spain, Hungary, Belgium and Portugal to test this hypothesis in the clinical population.

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