To the Editor:

We read with great interest the contribution by McIntyre1 outlining the importance of diagnosing and treating attention-deficit/hyperactivity disorder (ADHD) in bipolar patients. Concerning the common belief that stimulants may trigger a (hypo)manic or mixed episode or destabilize bipolar disorder in the long run, McIntyre argues that the avoidance of stimulants in bipolar disorder is not evidence based, because controlled studies are lacking. Therefore, the author supports the judicious use of stimulants in carefully selected bipolar patients in order to reduce comorbid ADHD symptoms.

We would like to support this view by reporting more recent data on stimulants in bipolar disorder. In addition, we would like to extend the point, because according to our recently proposed theory and some initial data,2,6 stimulants may even possess antimanic effects.

Three lines of evidence speak against the general reservation of using stimulants in bipolar patients: studies showing good tolerability of stimulants in ADHD patients, studies using adjunctive stimulants in bipolar patients treated with mood stabilizers, and case reports showing an acute antimanic effect of stimulants.

Given the high comorbidity of ADHD and bipolar disorder and the difficulties in differential diagnoses,5,26 one has to expect that many unrecognized bipolar patients have already been treated with stimulants due to their ADHD diagnosis. Driven by the fear that stimulants may trigger mania, studies using stimulants in ADHD were analyzed by the Food and Drug Administration, revealing that manic or psychotic reactions were rarely reported.4,14 Rather, in a recent randomized controlled trial (RCT) of methylphenidate an improvement in emotional dysregulation was shown parallel to amelioration of classical ADHD symptoms39 (see Galanter and colleagues42 for older trials). Another RCT analyzed the effects of methylphenidate and placebo in children with ADHD who also had comorbid severe mood dysregulation and elevated Young Mania Rating Scale (YMRS) scores, but did not reach all criteria for a bipolar diagnosis.38 No manic activation but a reduction of YMRS scores was shown, although the design of this study does not allow attributing the latter to the active drug alone.38

In children and adolescents with bipolar disorder, stimulants have been given to treat comorbid ADHD symptoms, which continued despite the improvement of manic symptoms by mood stabilizers. Open trials in children and adolescents showed that adding a stimulant to a mood-stabilizer regimen did not worsen but often improved bipolar symptomatology.37 One small controlled study is mentioned by McIntyre, in which 30 mood-stabilized children and adolescents with ADHD were given amphetamine salts or a placebo.40 The adjunctive stimulant improved ADHD without any worsening of manic symptoms. Similarly, two recent small RCTs did not show any provocation of manic symptoms when methylphenidate was added to a mood-stabilizer regimen.20,21

In adults, uncontrolled studies in patients with bipolar depression or residual depressive symptoms also showed good tolerability of stimulants.25 Concerning controlled studies in adults, only one small RCT (N=85) is available. Depressed bipolar patients treated with the stimulant modafinil in conjunction with a mood stabilizer did not show increased (hypo)manic symptoms.26 However, the use of additional hypnotics might be one reason for good tolerability of modafinil in this study,26 because lack of sleep can trigger and aggravate mania.42 Lack of sleep, however, is not necessarily a consequence of stimulant treatment, if patient and physician are aware of its importance. Furthermore, even an improvement of sleep efficiency under stimulant treatment has been shown in ADHD.29 More data on adjunctive stimulants in bipolar disorder will bring further RCTs, which are already underway.

In conclusion, recent data reviewed above supports the notion by McIntyre1 that the ananthematization of stimulants in bipolar disorder is an example of ideology over analysis, as the author put it. Now, large RCTs in bipolar patients are needed, not only for treating comorbid ADHD, residual fatigue, cognitive impairments, or the depressive phase in bipolar disorder, but also for the promising approach to use stimulants as an acute, immediately acting anti-manic drug, especially in those manic patients who are characterized by an unstable EEG vigilance.24

Sincerely,

Timlan Hensch, PhD
Hubertus Himmerling, MD
Ulrich Hegerl, MD

Reference

Response from the Author:

I would like to thank Drs. Hensch, Himmerich, and Hegerl for their comments. My interpretation of the available literature describing the use of psychostimulants in bipolar patients coheres in part with their observations and interpretations. I thought it was interesting that they further propose that stimulants might possess “anti-manic properties.” The authors base this on a pathogenetic model wherein disturbances in vigilance and regulation may subserve mania and attention-deficit/hyperactivity disorder (ADHD). My preliminary impressions of the authors’ proposal reminded me of an older literature describing the use of conventional unimodal antidepressants in patients with the treatment of mania (something I would strongly prescribe). It has been generally interpreted that the “anti-manic” effects of antidepressants was probably an epiphenomenon of cycle induction/acceleration, wherein the manic patient was iatrogenically mobilized into euthymia (and probably, in many cases, depression and rapid cycling).

As a clinical researcher, I have been struck by how frequently opinions on how to best treat bipolar patients is either not evidence based and/or perpetuated without any type of appropriate and rigorous appraisal. Examples are many, including but not limited to, the notion that conventional antidepressants are universally destabilizing, that benzodiazepines have a high abuse potential, leads to prolonged release of dopamine and engender and/or intensify bipolar phenomena. Taken together, the evidence base, my own clinical experience as well as diagnostic dilemmas that I frequently encounter in clinical practice, provide the impetus for a more refined subphenotyping of bipolar presentations so that we are better able to effectively treat symptoms and restore functioning. I will be watching closely the work of Hensch, Himmerich, and Hegerl, to see what their research concludes.

Sincerely,
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Varenicline-Induced Psychosis

To the Editor:

Varenicline is a novel therapeutic agent used for smoking cessation. It was launched in Turkey in 2008,2 2 years after receiving Food and Drug Administration approval in the United States.4 It is a selective partial agonist of presynaptic 4 2 neuronal nico- tinic acetylcholine receptors (nAChR) and leads to prolonged release of dopamine and norepinephrine. 4 2 nAChR is located in the mesolimbic pathway. By producing a moderate and sustained release of mesolimbic dopamine, it attenuates craving and withdrawal without producing its own dependence syndrome.5

Smoking is a major health problem among psychiatric patients and is associated with high morbidity and mortality.6 Promising drugs like varenicline may promote enthusiasm that a decline, if not a complete eradication, of such a serious problem exists in the near future. Actually, randomized clinical trials have demonstrated that varenicline increases the chances of successful long-term smoking cessation 2–3-fold compared with pharmacologically unassisted quit attempts.7

As is the case with most drugs, varenicline has some adverse effects. Among the common psychiatric side effects are insomnia, abnormal dreams, sleep disorder, and nightmares.5 The other infrequent side effects observed in randomized clinical studies include anxiety, depression, irritability, aggression, agitation, disorientation, disso-
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Letters

A 25-year-old man admitted to the emergency unit of our university hospital presented with the complaint that everybody was talking about him and accusing him of being responsible for the suicide attempt of a female client in the hotel where he worked. He had no reasonable explanation for why he would be the subject of such a scenario. Yet, had feelings of guilt and fear associated with it.

He reported that he felt fine until a couple of weeks prior, when he realized that clients who used to greet him in a friendly manner began to keep a distance from him. At the same time, he had palpitations and dyspnea that made him think he was going to die. Since then, he had nightmares and severe anxiety symptoms. At 19 years of age, while resting in his room, he started to hear sounds of prayer. At the same time, he had hallucinations and suicidal ideation and behavior.

Here, we present another case of varenicline-induced psychosis to add more to the current knowledge of this agent.

Case Report

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He reported that he felt fine until a couple of weeks prior, when he realized that clients who used to greet him in a friendly manner began to keep a distance from him. At the same time, he had palpitations and dyspnea that made him think he was going to die. Since then, he had nightmares and severe anxiety symptoms. At 19 years of age, while resting in his room, he started to hear sounds of prayer. At the same time, he had hallucinations and suicidal ideation and behavior.

Here, we present another case of varenicline-induced psychosis to add more to the current knowledge of this agent.

Discussion

The immediate question about this case is whether the psychotic symptoms had been induced by varenicline. One can speculate that prolonged release of dopamine and norepinephrine and shift of balance in cholinergic-adrenergic tone to the favor of adrenergic (mainly dopaminergic) tone may result in induction of psychosis. Others 14,15 share this hypothesis, but the actual mechanism is still unknown. Some intriguing problems need to be considered before this question can be answered.

Perhaps the primary problem deals with the very meaning and determination of an adverse effect. When a drug reaction is suspected, the clinician should determine whether the drug has been previously associated with that reaction. As mentioned above, there are similar case reports in the literature supporting an association between varenicline use and psychiatric adverse effects. However, there are also case series13-16 and studies of patients24,25 with chronic psychiatric disorders who showed significant improvement while taking varenicline in terms of smoking cessation without worsening of psychiatric symptoms. Furthermore, some authors also suggest that varenicline improves mood and cognition during smoking abstinence.

Further evidence is needed to conclude that the reaction, in our case psychosis, is a consequence of the drug. One factor is the temporal link; namely, a reaction observed during or immediately after the drug use, is highly suggestive of a relation. In published cases of varenicline-induced psychiatric adverse effects, the reported adverse effects have been seen within days to weeks of beginning varenicline. There is not a definite time period for varenicline to show its adverse effects, as was the case with our patient who developed psychotic symptoms after 30 days of varenicline use. The other evidence that supplements this association is improvement of the symptoms after the drug is discontinued. As pointed out, there was no improvement after 10 days of varenicline. Since the patient needed urgent intervention, it was not possible to wait for a possible spontaneous improvement.

Finally, the last supporting evidence is the elimination of other alternative explanations for the clinical picture. The patient gave a history of a past psychosis-like episode with auditory hallucinations together with symptoms of intense anxiety suggestive of panic attacks. The patient reported that the previous episode has improved spontaneously in a limited time without any significant intervention. Intense anxiety during psychotic process is not a rare condition. In this case, diagnosis of an anxiety disorder was ruled out, given the dominance of auditory hallucinations in the clinical picture. Considering the duration of symptoms, one can suggest that the case patient may have
suffered from schizophreniform disorder, which left him vulnerable to effects leading to psychosis. One may speculate that this episode is a recurrence of this underlying functional psychosis. The other possibility, which we believe to be the case, is that the psychosis was precipitated by varenicline use. It is also possible that an organic etiology is responsible for the symptoms. However, in light of the patient’s good physical health supported with normal laboratory and brain imaging results, this is not likely. One last possibility is the emergence of psychosis as a result of nicotine withdrawal. In fact, some emotional reactions may be observed during nicotine abstinence and may persist for several weeks. However, these reactions tend to peak a few weeks after cessation and commonly consist of depression, irritability, anxiety, and craving. Perception-like hallucinations are not common. In this patient, the main psychiatric findings, paranoia and auditory hallucinations, started nearly 4 weeks later. The time from the cessation of smoking until the beginning of psychosis as well as the psychotic findings, both rule out a mental status change of nicotine withdrawal.

We come back to the question of whether this was a case of varenicline-induced psychosis. We believe that after an account of all the possible explanations for the emergence of such a clinical picture, varenicline use is the most probable cause in this patient who already had a vulnerable biological substrate for psychosis.

Conclusion

The relationship between psychiatric reactions with varenicline treatment is still unclear. There is a need for independent community-based trials of varenicline to test its efficacy and safety in smokers with varying comorbidities and risk patterns. Until then, clinicians must be alert to these possible side effects and warn their patients about them. They should also consider other therapeutic interventions for patients who may be vulnerable to this agent.

Sincerely,

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References