STIMULANTS IN BIPOLAR DISORDER: BEYOND COMMON BELIEFS

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) hypomanic 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 an antimanic effect.

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,6-9 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.4,8 Rather, in a recent randomized controlled trial (RCT) of methylphenidate an improvement in emotional dysregulation was shown parallel to amelioration of classical ADHD symptoms10 (see Galanter and colleagues11 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.12 No mania 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.12

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.13,14 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.15 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.16,17 In adults, uncontrolled studies in patients with bipolar depression or residual depressive symptoms also showed good tolerability of stimulants.18-21 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.22 However, the use of additional hypnotics might be one reason for good tolerability of modafinil in this study,22 because lack of sleep can trigger and aggravate mania.23 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.24 More data on adjunctive stimulants in bipolar disorder will bring further RCTs, which are already underway.

In clear contrast to the reservation against stimulants, several case reports showed a rapid improvement of the manic symptoms in bipolar patients treated with psychostimulants.4,14 This finding is in line with the pathogenetic model we recently proposed that disturbed vigilance regulation can cause and/or perpetuate both manic behavior and ADHD.4,25 Most intriguingly, when studied in an environment with low external stimulation and eyes closed, manic patients show rapid declines to low vigilance stages and micro sleep within the first minutes of electroencephalogram (EEG) recording. In vulnerable subjects, this unstable vigilance regulation is thought to induce a behavioral syndrome with hyperactivity and sensation seeking as an auto-regulatory attempt to stabilize vigilance.26

In conclusion, recent data reviewed above supports the notion by McIntyre1 that the anathematization of stimulants in bipolar disorder is an example of ideology over analysis, as the author put it. Now, large RCTs 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

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Reference
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 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 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 benzdiphenazepines have a high abuse liability across most subpopulations of bipolar patients, and that “properly-treated” bipolar patients should receive monotherapy (the notion that tertiary bipolar patients can be treated effectively with monotherapy in most cases is perhaps one of the largest harms I have been exposed to).

There is no question that psychostimulants have not been sufficiently studied in bipolar disorder and it is not my view that they have been established at this point in time as generally effective and safe in bipolar populations. I do believe that as clinicians we should adhere to the principle of primum non nocere but consider ignoring literature that has reported in time as generally effective and safe in bipolar populations. I do believe that as clinicians we should adhere to the principle of primum non nocere but consider ignoring literature that has reported

Varenicline is a novel therapeutic agent for smoking cessation. It was launched in Turkey in 2008, 2 years after receiving Food and Drug Administration approval in the United States. It is a selective partial agonist of presynaptic 4, 2 neuronal nitrergic acetylcholine receptors (nAChRs) 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.

Smoking is a major health problem among psychiatric patients and is associated with high morbidity and mortality. 5 Promising drugs like varenicline may promote enthusiasm as 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. 5

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-
of a friend and without a prescription. After consulting a pharmacist 10 days prior, he had immediately stopped taking the drug. However, his symptoms still worsened and he was therefore presenting for psychiatric help at the current time.

A detailed inquiry of past psychiatric history revealed a brief episode of atypical psychosis, during which he experienced auditory hallucinations associated with 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 palpitations and dyspnea that made him think he was going to die. Since then, the combination of auditory hallucinations and intense anxiety symptoms continued in a wax-and-wane fashion, sometimes accompanied by insomnia and irritability. A few times, these symptoms got so intense that he had to spend the night in the emergency room. After consulting an internist who said the symptoms were not organic in origin, the patient visited a psychiatrist who treated him with alprazolam. He stopped taking this medication after a short time because he did not find it to be helpful. Although he sought no other professional help, his complaints resolved spontaneously and disappeared completely at the end of 3 months. He experienced no other psychiatric symptom or related delusions of reference and guilt leading to feelings of intense anxiety and fear. Laboratory results were in normal limits and electroencephalogram and cranial magnetic resonance imaging showed no pathological findings. Thus, the most probable reason for this psychotic episode was the combination of auditory hallucinations and interrelated delusions of reference and guilt. The patient displayed no other psychiatric symptoms except for auditory hallucinations and intense anxiety symptoms. Furthermore, some authors also suggest that varenicline improves mood and cognition during smoking abstinence.3,4

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 off 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 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 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 series22,23 and studies of patients22,23 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.3,4

The immediate question about this case is whether the psychotic symptoms had been induced by varenicline. One can speculate that prolonged release of dopaminergic effect was of particular significance.8,9,10 Other cases reported recurrences of either manic or depressive episodes in patients with mood disorders.9,14 One case report involved a schizophrenia patient presenting with exacerbation of psychotic symptoms.5 Although the abovementioned adverse effects have been observed mostly in people with positive psychiatric history, they may occur in those with no preexisting psychiatric disorder as well.15 In light of these case reports, the US FDA issued public health advisory notes reporting a possible association between varenicline and an increased risk of behavior change, agitation, depressed mood, and suicidal ideation and behavior.15

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

Case Report

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. He said they were whispering among themselves and making meaningful gestures in a way that made him think he had done something wrong. Day by day, this impression turned into a certainty as he began to hear them talk louder, even in the absence of anyone other than himself. He said he finally understood that the reason why everybody was acting so strangely was that they thought he was responsible for the suicide of a female English tourist. However, there was no official news about such a suicide, which for him seemed to be a part of the plot. His feelings of guilt were sometimes so unbearable that he thought it would be better to die, but made no suicide attempt. He recalled having taken the drug varenicline to quit smoking for 30 days. He had started to take this drug twice daily with the advice of a friend and without a prescription. After consulting a pharmacist 10 days prior, he had immediately stopped taking the drug. However, his symptoms still worsened and he was therefore presenting for psychiatric help at the current time.

A detailed inquiry of past psychiatric history revealed a brief episode of atypical psychosis, during which he experienced auditory hallucinations associated with 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 palpitations and dyspnea that made him think he was going to die. Since then, the combination of auditory hallucinations and intense anxiety symptoms continued in a wax-and-wane fashion, sometimes accompanied by insomnia and irritability. A few times, these symptoms got so intense that he had to spend the night in the emergency room. After consulting an internist who said the symptoms were not organic in origin, the patient visited a psychiatrist who treated him with alprazolam. He stopped taking this medication after a short time because he did not find it to be helpful. Although he sought no other professional help, his complaints resolved spontaneously and disappeared completely at the end of 3 months. He experienced no other psychiatric symptom or related delusions of reference and guilt leading to feelings of intense anxiety and fear. Laboratory results were in normal limits and electroencephalogram and cranial magnetic resonance imaging showed no pathological findings. Thus, the most probable reason for this psychotic episode was the combination of auditory hallucinations and intense anxiety symptoms. Furthermore, some authors also suggest that varenicline improves mood and cognition during smoking abstinence.3,4

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suffered from schizopeniform 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.25 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.26 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**


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