STIMULANTS IN BIPOLAR DISORDER: *BEYOND COMMON BELIEFS*

To the Editor:

We read with great interest the contribution by McIntyre[1] 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,[4,7] 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.[8-12] Rather, in a recent randomized controlled trial (RCT) of methylphenidate an improvement in emotional dysregulation was shown parallel to amelioration of classical ADHD symptoms[13] (see Galanter and colleagues[14] 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.[15] 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.[15]

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.[16,17] 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.[18] 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.[19,20]

In adults, uncontrolled studies in patients with bipolar depression or residual depressive symptoms also showed good tolerability of stimulants.[21-25] 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,[27] because lack of sleep can trigger and aggravate mania.[4,28] 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 clear contrast to the reservation against stimulants, several case reports showed a rapid improvement of the manic symptoms in bipolar patients treated with psychostimulants.[3,5] 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.[2-4] 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 autoregulatory attempt to stabilize vigilance by increasing external stimulation (a similar syndrome can be observed in overtired children). This autoregulatory mechanism can override the physiological tendency to seek sleep, thereby aggravating the sleep deficits and worsening the vigilance instability. Thus, a vicious circle is started, resulting in full-blown mania.

In conclusion, recent data reviewed above supports the notion by McIntyre[1] that the anathematization of stimulants in bipolar disorder is an example of ideology over analysis, as the author put it. Now, large RCTs of stimulants 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.[3,6]

Sincerely,

Tilman Hensch, PhD
Hubertus Himmerich, MD
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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 the treatment of mania (something I would strongly proscribe). 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 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 myths 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* and assure that the safety of medications is well established before we widely prescribe them. It would be naive and thoughtless to consider ignoring literature that has reported on possible destabilization in bipolar disorder with psychostimulants. Nevertheless, these observations have to be confirmed or refuted with rigorous science. In my article, I have referred to the triumph of ideology over analysis that so often occurs in bipolar disorder (and other psychiatric/medical conditions), with the anathematization of stimulants being an exemplar.

At this point in time, largely based on my clinical experience, I would not be comfortable prescribing a psychostimulant to a patient presenting with a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition-defined manic or mixed episode (I typically prescribe them in patients who are euthymic and/or experiencing depressive symptoms/episodes with concurrent ADHD symptomatology). That being said, I have been struck at how often I meet patients who present with various "mixity" phenotypes (eg, depressive mixed states, mixed hypomania) and report a beneficial effect of stimulants. Moreover, the beneficial effect is corroborated by mood charting as well as third party observations. I have also noticed that in many patients it is this very phenotype wherein stimulants may engender and/or intensify bipolar phenomenology. 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,[1] 2 years after receiving Food and Drug Administration approval in the United States.[2] It is a selective partial agonist of presynaptic a_4b_2 neuronal nicotinic acetylcholine receptors (nAChR) and leads to prolonged release of dopamine and norepinephrine. a_4b_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.[3]

Smoking is a major health problem among psychiatric patients and is associated with high morbidity and mortality.[4] 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.[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.[6] The other infrequent side effects observed in randomized clinical studies include anxiety, depression, irritability, aggression, agitation, disorientation, disso-

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ciation, decreased libido, and mood swings.[3,5] Of note, these studies excluded subjects with common psychiatric diagnoses.

After varenicline became available for clinical use, cases reporting serious psychiatric adverse effects associated with its use began to emerge in the literature. Reports of suicidal ideation and behavior are of particularly alarming significance.[7,8] 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.[15] Although the abovementioned adverse affects have been observed mostly in people with positive psychiatric history, they may occur in those with no preexisting psychiatric disorder as well.[16] 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.[17]

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 problem until this index episode.

During this first encounter and the following two evaluative visits, the patient displayed no other psychiatric symptoms except for auditory hallucinations and interrelated 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 seemed to be varenicline. Actually, the application of the Naranjo citeria[18] also revealed a probable association. The patient was immediately started on oral antipsychotic treatment with olanzapine 10 mg/day, which initially ameliorated his anxiety and gradually improved his delusions. After 20 days he felt well enough to go back to work. He was no longer worried about other people's behaviors, but still believed that what he had experienced was real.

The patient gave consent for publication of this case report after being adequately informed.

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 series[19-21] and studies of patients[22,23] 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.[24]

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 suggest that the case patient may have

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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.[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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