The Controversial Case of Biperiden
From Prescription Drug to Drug of Abuse

To the Editors:

Anticholinergic drugs such as biperiden are commonly used in psychiatry for the prophylaxis and treatment of extrapyramidal symptoms caused by antipsychotics, as well as for tremors in Parkinson disease. Anticholinergic abuse has been reported in nonpsychotic patients probably because of inducing mild euphoria with increased sociability and energy through an increase of dopaminergic activity.[1–3]

Since 1960, anticholinergic abuse has been described in various countries by individuals taking them without prescription.[4,5] Recent evidence from the literature is mainly limited to low- and middle-income countries such as Saudi Arabia, Jordan, Iraq, and Brazil, and patients described are often unmarried, unemployed, marginalized, smokers, polysubstance abusers, and with a positive family history for mental disorders. Prisoners, adolescents, and heroin abusers seem to represent the highest risk populations.[3,6]

Recently, this phenomenon has also been observed in Italy, mainly in immigrants from North Africa. However, biperiden abuse is also growing among native Italians (Table 1).[7]

We present the case of a patient with anticholinergic abuse. A 27-year-old Tunisian man came to Italy in 2010. He reported a previous history for polysubstance abuse (including trihexyphenidyl, an antimuscarinic drug). When initially seen in a prison dispensary in May 2013, he reported having used clonazepam 8 mg/d, cocaine (3 times/wk), cannabis, and alcohol since his arrival in Italy. The patient met *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition*, *Text Revision* criteria for polysubstance dependence. Therefore, he was treated with diazepam 20 mg/d to prevent alcohol and benzodiazepine withdrawal syndromes and he denied adverse effects to this therapy. In the next few days, after the abrupt discontinuation of the different substances that he was using before the imprisonment, he reported increasing dysphoria, mild psychomotor agitation, anxiety, headache, and difficulty falling asleep and he requested biperiden.

The psychiatrist denied that medication, until the patient started to deliberately cut his arms to induce the physician to prescribe him the drug. Therefore, biperiden (4 mg/d in the evening) was prescribed. One week after the initiation of this treatment, he reported improved mood, reduced agitation, decreased anxiety, and regularization of his sleep-wake schedule and the prescription was refilled for months at the same dose. Six months later, the patient was admitted to the hospital emergency service because of an episode of acute urinary retention with vesical globe that required catheterization. He reported that he was consuming biperiden 16 mg/d, illegally obtained from other prisoners. Despite the potential adverse effects, he admitted being unable to give up this drug because of intense dependence and fear of withdrawal symptoms. The patient met the following 4 of the 7 *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition*, *Text Revision* criteria for biperiden dependence: he showed tolerance because he had been increasing the dose up to 16 mg daily (criteria 1); he was taking biperiden in such an amount that he developed severe adverse effects (criteria 3); he was reporting persistent desire and unsuccessful efforts to cut down the dosage (criteria 4); and despite having suffered from a vesical globe, he admitted to be unable to stop (criteria 7). The mental status examination revealed a mild confusional state with temporal and spatial disorientation and impairment of attention and concentration that precluded the possibility to complete a mini-mental status examination. Moreover, the patient suffered from psychomotor agitation; the speech was only partially informative with disorganization of thought, although delusions or perceptual disturbances were not present. Three days after, the patient was released from the emergency department and was readmitted back to the prison. Biperiden was gradually tapered from 16 to 4 mg/d with reductions of 4 mg/wk. After a period of initial compliance without any symptom, the patient reported craving, mild dysphoria, fatigue, lack of motivation, and insomnia. Therefore, the patient was treated with quetiapine, 50 mg/d, and only after 6 months, he definitely stopped using biperiden.

The case we described underlines a widespread phenomenon probably underestimated by recent epidemiological studies.[8] The marked increase of anticholinergic abusers among both immigrants to Italy and its native population has important therapeutic and diagnostic implications: anticholinergic abusers do not necessarily access substance abuse services and thus they frequently do not receive adequate diagnosis and treatment. Different pharmacological effects of antimuscarinic drugs could justify the drug-seeking behavior described in our report. Firstly, there is evidence that the blockade of the cholinergic receptors enhances striatal dopamine release. The resulting dopaminergic hyperactivity could be responsible for both the psychotomimetic effects reported by the abusers (euphoria, elevated energy and mood, increased social interactions) and for the toxic syndrome described with higher doses of central anticholinergics (delirium, visual hallucinations, confusion, dream-like state, apraxia, agnosia, amnesia, and intellectual impairment). In this abuser at the beginning of the incarceration period, the biperiden was requested to obtain its psychotomimetic effects. Secondly, antimuscarinic drugs seem to induce rapid tolerance to the euphoriant effects

TABLE 1. Nationality of Biperiden Abusers Attending Substance Use Disorders Service of Parma Inside and Outside Prison.

	Biperiden Abuse				Fisher Exact Test
	Yes		No		
	n (%)		n (%)		*P*
SUD service					<0.001
Inside the prison (N.116)	18	15.5	98	84.5	
Outside the prison (N.725)	9	1.2	716	98.8	
Nationality					<0.001
Italian (N.729)	9	1.2	720	98.8	
Non-Italian (N.112)	18	16.1	94	83.9	
North-African (N.57)	16	28.0	41	72.0	

Adapted from *Substance Use Disorders Service Anonymized Administrative Database*. Parma, Italy: Mental Health and Addiction Department, Azienda Unità Sanitaria Locale of Parma; 2014.[7]

SUD indicates substance use disorder.

that promotes the abuse and dependence mechanisms. The clinical reports of patients who increased the doses of anticholinergics to achieve the mood-elevating effects support that there might occur a pharmacological tolerance to M1 antagonist.[9–13] This hypothesis is also suggested by the finding that tolerance to the biperiden inhibiting effect of REM sleep can develop after treatment.[14,15] Anticholinergic abusers develop a "cholinergic overdrive" (a complex of symptoms secondary to the withdrawal of muscarinic blockade and attributed to the upregulated cholinergic receptor unmasking). The clinical presentation includes dysphoria, anxiety, fatigue, insomnia with terrifying dreams, myalgia, malaise, diaphoresis, paresthesia, coryza, gastrointestinal distress, and headaches and it is described as a rapid symptoms resolution after giving biperiden.[4] Therefore, our patients, after a short period, would have continued to abuse biperiden to avoid withdrawal symptoms rather than to achieve the pleasurable effects. The third point of discussion concerns the role of acetylcholine in learning and memory. Consolidated research demonstrated that the blockade of muscarinic receptors impairs the encoding of new memories.[16] Recent animal studies reported that biperiden blocks the consolidation of cocaine conditioned place preference (CPP),[17] which is a learned behavior that occurs when a subject comes to prefer 1 place more than others because the preferred location has been paired previously with rewarding events. Typically, drugs of abuse such as cocaine produce CPP. Thus, in this abuser, biperiden might have had a positive effect on addictive behavior reducing the conditioned learning and consequently reducing the reinforcing effects of cocaine.[18] Finally, this observation confirms that the occurrence of adverse effects of anticholinergics is dose dependent; the peripheral effects of biperiden appear only rarely in our population of abusers and the patient described was 1 of the rare ones who had adverse effects. Another possible explanation of the infrequency of the peripheral effects could be that many of the troublesome effects of these drugs result from interaction with specific receptor subtypes. Considering that biperiden is a selective muscarinic M1 antagonist and that the M1 receptor is the most significant receptor in the central nervous system, there is the possibility that biperiden, at low doses, has the central nervous system as its specific target.

Further studies are needed to estimate the impact of biperiden as a substance of abuse, especially among marginalized people. Concerning Italy, the preliminary data presented in Table 1 support that biperiden is particularly abused by prisoners coming from North-African countries. The high prevalence in this population could be attributed both to the strong law enforcement efforts that have been the customary approach to cannabis, opiates, and cocaine consumption in North African countries and to the low prices and the easier availability of antimuscarinics compared with other substances of abuse on the black market. These environmental conditions push the abusers to shift to the more disposable and cheaper substances that are associated with the brain mechanisms of abuse and dependence. Interestingly, some prisoners reported that the anticholinergic drug was the only substance abused before incarceration. To shed a light on the specific brain mechanisms underlying anticholinergic abuse and dependence, patients with isolated "primary" abuse of biperiden are worth identifying.

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