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AM. J. DRUG ALCOHOL ABUSE, 18(4), pp. 399–406 (1992)

Abuse of Monoamine Oxidase Inhibitors

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ABSTRACT

Monoamine oxidase inhibitors, like other antidepressants, generally are considered free of risk for abuse. There is, however, some evidence that MAOIs possess dependence and abuse potential for some patients. We will review the available literature and describe three current cases. Recommendations for treatment are discussed briefly.

INTRODUCTION

Antidepressants are considered to be an important, effective, relatively safe, nonaddictive class of therapeutic agents in psychiatry, and are considered free of potential for abuse. While accurate for tricyclic and heterocyclic antidepressants, evidence is accumulating that monoamine oxidase inhibitors may carry an abuse risk for some patients. In this article we will briefly review the history of monoamine oxidase inhibitors, the reports of their abuse, and describe three cases of ours relevant to this subject.

The antidepressant effects of MAOIs were a serendipitous discovery resulting from the use of ipromiazide in the treatment of tuberculosis. In 1952 Zeller and coworkers [1] found that monoamine oxidase was inhibited by this medication and shortly thereafter researchers [2] noted improved mood in ipromiazide-treated tuberculosis patients. This mood-elevating effect was confirmed by studies in depressed patients [3, 4]. Ipromiazide use, however, was discontinued because of its hepatoxicity. Tranylcypromine, a nonhydralazine MAOI, was introduced

in the late 1950s. Its structure is similar to that of amphetamine, as it was synthesized in an attempt to develop a less problematic stimulant. It was noted to produce significant monoamine oxidase inhibition.

Due to the potential risk from hypertensive crisis, MAOIs fell into disuse in the 1970s. However, because of their effectiveness in some otherwise unresponsive depressed patients, there has been a resurgence in their use. They now are recommended by some for a variety of other psychiatric conditions besides depression, including panic disorder and eating disorders.

LITERATURE CASE REVIEW

Over the years of their use, a small but steadily growing number of cases of MAOI dependence and abuse have been reported. (See Table 1.)

The first case was reported in 1963 by Mielezarek and Johnson [5]. They described a case of a woman with a diagnosis of hysterical personality who was treated with tranylcypromine for anxiety and depression. She increased her intake of tranylcypromine from 80 to 140 mg/d, had possible withdrawal symptoms when the medication was stopped, and thereafter evidenced drug-seeking behavior with attempts to gain prescriptions from multiple practitioners.

Le Gassicke [6], also in 1963, described a case of tranylcypromine dependence in a 24-year-old man with a severe personality disorder but no past history of drug abuse. He was ingesting up to 200 mg/d when he began to show hypomanic symptoms. He acquired the medication through abuse of prescriptions. He had been tried previously on phenelzine with no effect. In a subsequent article Le Gassicke et al. [7] demonstrated that upon withdrawal of tranylcypromine this patient exhibited a sleep pattern that was typical of amphetamine withdrawal.

Shopsin and Kline [9] in 1976 reported three cases of tranylcypromine dependence. Tolerance developed to the "stimulant-energizing amphetamine-like effect, with progressive self-dose buildup (i.e., 'abuse')." Despite doses of up to 300 mg/d, minimal or no side effects occurred even when contraindicated foods or medications were taken. The one patient who they described in detail was a 52-year-old man with a past history of amphetamine abuse.

Ben-Arie and George [10] in 1979 described one case of tranylcypromine dependence. The patient, a 47-year-old man with a history of problematic amphetamine, barbiturate, and alcohol use, had been prescribed tranlycypromine for depression. After an initial good response to therapeutic amounts, he developed tolerance and increased his dose to 300 mg/d. With reduction or cessation of the medication, he experienced anergia, depression, confusion, and hallucinations.

Case	Age	Sex	Diagnosis or symptoms	Drug	Dose (mg)	Withdrawal symptoms	Relapse	Tolerance	Meets criteria for	
									Dependence	Abuse
1963	24	F	Hysterical personality depression	Tranylcypromine	140	Acute tension	Yes	Not specified	Yes	
1963	24	M	Personality disorder, shy and solitary depression	Tranylcypromine	200	Not specified	Not specified	Not specified		Yes
1976[a]	52[b]	M	Characterologic problems, sociopathic behavior, amphetamine, alcohol, barbituate abuse	Tranylcypromine	300	Confusion, weakness, sweating, tachycardia, nausea, and vomiting	Expressed desire for high MAOI dose not specified if relapsed	Yes, tolerate high tyramine content foods	Yes	
1979	47	M	Depression, abuse of amphetamine and barbituates	Tranylcypromine	300	Anxiety, confusion, visual and auditory hallucinations for 12 days	Yes	Yes, tolerance to therapeutic effects	Yes	
1981	33	F	Depression, personality disorder (unspecified)	Tranylcypromine	300	Unspecified	Yes	Not specified		Yes
1981	34	M	Anxiety, depression, alcohol abuse	Tranylcypromine	150	Headaches, diarrhea, weakness, depression, and anxiety	Yes	Not specified		Yes
1981	65	M	Alcohol abuse	Tranylcypromine	300	Anxiety	Yes	Not specified		Yes
1981	39	M	Depression, past alcoholic	Tranylcypromine	200	Anxiety, generalized aches for 10 days	Not specified	Not specified		Yes
1989	34	M	Atypical depression, generalized anxiety disorder, adult addiction, drug abuse	Tranylcypromine	120	Abdominal cramps, diarrhea, irritability, fatigue, feeling shaky, poor sleep, trouble concentrating	Yes	Not specified	Yes	
1973	?	?	?	Tranylcypromine	?	?	?	?	?	?
1974	30s	M	Neurotic depression	Phenelzine	[c]	Headaches, shivering feelings of cold × 7d	—	Yes	Yes	
1974	[d]	F	Neurotic depression	Phenelzine	[c]	Depression, irritability, cold and shivering	—	Yes	Yes	

[a]3 cases. [b]Not specified in 2 cases. [c]No abuse. [d]Not specified.

Griffin et al. [11] in 1981 report four cases of tranylcypromine abuse. These patients were of both sexes with ages ranging from 33 to 65 years old. Three of the four had past histories of substance abuse. All were taking from 200 to 300 mg tranylcypromine daily.

Westermeyer [12] in 1989 described one patient, a 34-year-old man, who abused tranylcypromine by taking 120 mg/d. He had past diagnoses of atypical depression, dysthymia, generalized anxiety, and adult residual of attention deficit disorder. He had a past history of alcohol and stimulant abuse. When the tranylcypromine was stopped, he experienced withdrawal symptoms of abdominal cramps, vomiting, diarrhea, irritability, fatigue, and a shaky feeling inside.

One additional report of tranylcypromine abuse is noted in a broad study of drug abuse. Swanson et al. [13] summarized experience with 225 patients who required psychiatric hospitalization for treatment of prescription drug abuse. One of this series was misusing an MAOI, tranylcypromine, but clinical details were not provided.

Pitt [8] in 1974 reported two cases of possible withdrawal symptoms of phenelzine. These patients experienced "shivering and a feeling of intense cold lasting over a week that was reminiscent of the 'cold turkey....'" These patients had not abused the medication.

In all, the literature describes 12 cases of tranylcypromine abuse. They are fairly evenly divided between men and women and span an age range from mid 20s to mid 60s. At least one-half had a prior history of substance abuse. Several cases described withdrawal symptoms. Two cases of possible withdrawal symptoms to the abrupt discontinuance of phenelzine are reported, but no actual cases of phenelzine abuse.

CASE REPORTS

In our experience we have treated three cases of phenelzine abuse. They will be described briefly, with current clinical data where known. In our first case (Case 1) a 21-year-old man presented with a exacerbation of long-standing symptoms of depression. The patient had never been hospitalized psychiatrically, but had had multiple unsuccessful, non-MAOI antidepressant trials. He had no current or past history of mania, psychosis, or alcohol or drug use. Initial mental status was unremarkable except for findings of nonpsychotic depression. Physical examination and lab studies were within normal limits.

The patient, who had been hospitalized, was started on phenelzine which was gradually increased to 90 mg/d. His sleep, appetite, and mood soon improved.

However, midway in his hospitalization he became uncharacteristically preoccupied with psychodynamic interpretations of his illness to which he ascribed unrealistic expectations. He also requested increasing doses of phenelzine which he was convinced improved his insight. He became grandiose about solving his personal and family problems. His phenelzine dose was decreased to 75 mg with improvement in his judgment and remission of his hypomanic symptoms. He was discharged with a diagnosis of atypical depression and borderline personality disorder. He was given specific instructions not to exceed 75 mg of phenelzine per day, and appropriate follow-up was arranged.

Within a month after discharge, the patient again was inducing manic states by purposefully ingesting excessive amounts of phenelzine of up to 120 mg/d. The medicine was obtained by simultaneously visiting multiple clinics and crisis centers. He was repeatedly hospitalized in manic and hypomanic states. Two years after his initial hospitalization, he had continued unremittently his abuse of phenelzine. Four years later, however, he had stopped using phenelzine and was admitted for another medication trial. He blamed his physician and his first hospitalization for his "addiction" and subsequent troubles.

The second case (Case 2) is that of a 35-year-old pharmacist who suffered from depression and bulimia. Her depression was characterized by low self-esteem, suicidal ideation, alternating hypo- and hypersomnolence, and food craving. She had no history of substance abuse, mania, or psychosis. She was unresponsive to non-MAOI antidepressants, and therefore was tried on phenelzine. Shortly after reaching 75 mg/d of phenelzine, she became agitated, hyperactive, grandiose, verbally aggressive, demanding, and directive with others. This resulted in severe conflicts at work and in her personal relationships, and her bulimia became worse. It was learned later that she supplemented the phenelzine herself in amounts over 90 mg/d which, when it was discontinued because of the hypomanic state, she continued to self-administer. She only stopped it after jeopardizing herself at work and since then has readministered it to herself episodically with the same untoward results. Each time she initially was blind to the deleterious effect that it had upon her.

In the third case (Case 3) a 31-year-old, thrice married, employed woman had a 22-year history of depression and a prior history of polydrug abuse. She had been previously treated with ECT as well as with a series of non-MAOI antidepressants, antipsychotics, and antianxiety agents. She was hospitalized, treated with 75 mg phenelzine, and was discharged much improved after a brief admission. Four months later she was readmitted with anxiety, feelings of worthlessness and insecurity, and psychotic symptoms including "electricity in my blood running up and down my body," auditory and visual hallucinations, paranoia, and bizarre

sensations. After several days she admitted to taking from 90 to 150 mg phenelzine daily in addition to using alcohol and marijuana. Although her psychotic symptoms resolved rapidly with decreasing doses of phenelzine, she was very resistant to doses of less than 60 mg daily. She complained that she felt depressed and anxious and missed the stimulant quality of higher doses.

DISCUSSION

The DSM-III-R diagnostic class for Substance Use Disorders deals with the symptoms and maladaptive behavioral changes associated with use of psychoactive substances affecting the central nervous system [14]. The diagnosis of dependence requires that at least three of nine criteria are met. While psychoactive drugs have some characteristics in common, their effects and individual reactions to them can vary widely. The criteria used to diagnose the disorders of dependence and abuse are based upon response patterns of the user, not simply the use of a psychoactive substance. Substance abuse is a residual category for maladaptive patterns of psychoactive drug use which do not meet the criteria for dependence. These cases suggest that both phenelzine and tranylcypromine have dependence and abuse potential.

The literature to date describes 12 cases of MAOI misuse, all involving tranylcypromine. Two instances were noted where the abrupt discontinuation of phenelzine may have produced withdrawal symptoms. Table 1 summarizes clinical features of the literature cases including whether the DSM-III-R criteria for a diagnosis of substance use disorder, either abuse or dependence, was met. We have reported three additional cases, and the first to our knowledge in which the abused MAOI was phenelzine. In all instances where sufficient data were available (11 of 12 literature cases and the three cases of ours), the patterns of misuse of MAOIs directed a DSM-III-R diagnosis of a substance use disorder. The medications were used in excessive amounts, exceeding therapeutic ranges and safety limits, and often with disregard for potential or actual harmful results. Several of the reported cases combined high tranylcypromine doses with pressor medications and foods with high tryamine contents. These risky behaviors, which remarkably produced no untoward results, suggest the probability that tolerance had developed to some effects of the MAOI. In other cases, however, evidence of physical and psychiatric effects of the excessive dosage (irritability, anger, and teeth grinding) persisted, and suggest that tolerance had not developed to these side effects. The patient in the case reported in 1979 seemed to develop tolerance to the therapeutic effects of tranylcypromine as well. He needed to

increase the dosage to excessive amounts to maintain the improvement that initially occurred within the therapeutic range.

Relapse following withdrawal from excessive MAOI use was a significant problem. When commented upon in the literature, every case had difficulties with relapse. These alone totaled 50% of all cases. With our cases of phenelzine abuse, in each instance relapse occurred or was imminent, and for two of the patients it became a chronic problem.

Symptoms of withdrawal from MAOIs were frequent and suggestive of more than solely reemergence of the primary illness. The majority of tranylcypromine-abusing patients experienced withdrawal symptoms that in the aggregate included anxiety, depression, confusion, hallucinations, tremulousness, nausea, vomiting, diarrhea, and chills. While the appearance of anxiety and depression may have reflected the resurfacing of the primary psychiatric disorders for which the MAOIs were taken, the others are compatible with withdrawal symptoms. Two reports link the abrupt discontinuation of phenelzine to symptoms characteristic of withdrawal. In our own case of phenelzine abuse, doses were tapered rather than abruptly stopped, reducing the likelihood of frank withdrawal symptoms. These patients, however, did evidence both reemergence of their original symptoms and psychological dependence. They missed the mental state induced by the excessive doses to which they repeatedly returned despite the development of hypomanic and manic symptoms with severe sequelae.

That antidepressants including MAOIs occasional can induce mania is well recognized; it usually is regarded as an unwelcome side effect by patients as well as clinicians. In this cohort, however, the effect was actively sought by patients who were unaware of the deleterious consequences, or for whom they were no deterrent. The drug-seeking behaviors and medication responses evidenced in these examples have characteristics similar to those seen in stimulant abuse. MAOIs share some of the pharmacologic effects of stimulants, and in vulnerable patients seem to share their potential for abuse as well. Levels of norpinephrine, dopamine, and serotonin present at nerve junctions are increased by MAOIs. Similar actions are thought to be important in producing the mood altering and abuse appeal of stimulant such as amphetamine and cocaine [15].

As MAOI use increases for a variety of disorders, this problem may become more apparent. While there are no specific predictors of abuse, two factors are disproportionately but not invariably present in the past histories of the patients who evidence dependence: prior substance abuse or a more severe character disorder. In patients presenting with such characteristics, additional care and monitoring may be indicated if MAOIs are to be used.

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AM. J. DRUG ALCOHOL ABUSE, 18(4), pp. 407–428 (1992)

Assessing Treatment Effects through Changes in Perceptions and Cognitive Organization

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ABSTRACT

This investigation tested the Associative Group Analysis (AGA) for its analytic sensitivity in assessing perceptions and attitudes and in mapping changes in cognitive organization indicative of substance abuse. Based on inferences drawn from the distributions of thousands of spontaneous, free associations elicited by strategically selected stimulus themes, AGA offers an unstructured approach to assess images and meanings, and to map systems of mental representation evasive to the more direct methods of using questions or scales. This article compares pretreatment and posttreatment samples, tracing the psychosocial effects of treatment. The investigations focus on variables related to substance abuse such as self-image, social nexus, and perceptions of illicit substances. The results indicate a sensitive approach, useful in treatment evaluation.

BACKGROUND: FAILING EXPECTATIONS

In recent decades, researchers interested in the psychological effects of drug use have focused primarily on personality traits. They assumed that psychological effects of habitual drug use may be best identified by measuring changes in some relevant personality traits. This approach followed, rather naturally, from the high status of personality constructs in psychology, and the inconclusive findings came as a surprise.