

# Letters to the Editor

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## Internet Pharmacy Prescription and Phentermine Overdose

**Sir:** The Internet is now widely used by patients for both health information and prescription services. Yet, a MEDLINE search in January 2002 using the phrase "Internet pharmacy" showed a total of 99 articles; nearly all were geared toward health care management or the general public. There are only a few published reports of bad outcome resulting from medical information obtained from the Internet.<sup>1</sup> The U.S. Food and Drug Administration noted 326 Internet sites selling pharmaceutical products.<sup>2</sup> The exact numbers are difficult to quantify as Web sites are constantly changing. I report a case of overdose with phentermine that was obtained through an Internet pharmacy.

**Case report.** Ms. A, a 20-year-old woman with a prior history of anorexia nervosa, was admitted to the intensive care unit (ICU) after an unintentional overdose of phentermine. She denied suicidal intent and history of bulimia, depression, or suicide attempts. She reported ingesting a total of 15 tablets of phentermine (37.5 mg) over the course of 8 hours to curb appetite. She had ordered phentermine using the Internet, with no direct patient-physician contact. The prescription was signed by an out-of-state physician; the pharmacy was in yet another state.

Initial presentation was significant for pressured speech, tactile hallucinations of bugs on her skin, and visual hallucinations of black dots. She rapidly progressed to refractory seizures, which were treated with the following medications: diazepam, 10 mg; diphenhydramine, 25 mg; lorazepam, 2 mg; fosphenytoin, 1 g; and propofol infusion. She recovered fully in 48 hours with supportive care in the ICU and was discharged home with outpatient psychiatric follow-up.

Phentermine is a centrally acting amphetamine drug widely known for weight reduction in combination with fenfluramine ("fen-phen"). Although fen-phen has been withdrawn owing to cardiac valvular disease and pulmonary hypertension,<sup>3</sup> phentermine alone is still available. Phentermine, like other amphetamine drugs, has significant adrenergic effects. Previous reports of phentermine toxicity have involved chronic use rather than acute ingestion.<sup>4</sup>

The Internet has provided a means for physicians to prescribe without direct knowledge of the patient, a deviation from the usual standard of practice. In addition, pharmacies can attempt to circumvent the usual regulatory systems. Fortunately, legislation has been proposed in many states to limit such drug sales.<sup>5</sup>

Since physicians and pharmacies unrelated to the local community may be prescribing and dispensing medications that can then be used in overdose, psychiatrists will need to ask patients about pharmaceuticals obtained through the Internet to

complete the medication database. Of course, patients can abuse any medications, so collaboration between pharmacies and physicians is essential to minimize this risk.

*Dr. Takeshita reports no financial or other relationship relevant to the subject matter of this letter.*

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## Ziprasidone Augmentation of Clozapine in 11 Patients

**Sir:** Clozapine, the oldest atypical antipsychotic, remains the "gold standard" in the treatment of schizophrenia and associated psychotic disorders.<sup>1</sup> However, the side effects of clozapine are well known and include significant weight gain and an anticholinergic profile.<sup>2</sup> The concept of adding quetiapine to clozapine with the potential to lower the dose of clozapine and thus reduce its side effect profile has been supported clinically and in the literature.<sup>3,4</sup>

Ziprasidone has been available in the United States since March 2000. The unique side effect profile of this compound includes minimal anticholinergic side effects and weight neutrality. Additionally, the major metabolic pathway for ziprasidone is via aldehyde oxidase, for which there are no known inducers or inhibitors.<sup>5-8</sup> Thus, the ability to safely add ziprasidone in patients currently on clozapine treatment is especially attractive. As such, ziprasidone becomes the logical candidate for clozapine augmentation. This letter reports on my clinical experience with ziprasidone augmentation of clozapine.

Eleven patients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, all of whom were stable on a clozapine regimen for a minimum of 8 years, gave verbal consent to try augmenting their regimen of clozapine on an open-label, voluntary basis. The hope was for a reduction in apathy and an

**Table 1. Clozapine Doses Before and After Augmentation With Ziprasidone, 160 mg/day**

| Patient   | Age (y) | Sex | Original Clozapine Dose (mg/day) | New Clozapine Dose (mg/day) |
|-----------|---------|-----|----------------------------------|-----------------------------|
| 1         | 31      | M   | 900                              | 600                         |
| 2         | 36      | F   | 600                              | 300                         |
| 3         | 49      | M   | 900                              | 400                         |
| 4         | 29      | M   | 900                              | 600                         |
| 5         | 40      | M   | 900                              | 450                         |
| 6         | 32      | F   | 900                              | 400                         |
| 7         | 31      | M   | 800                              | 600                         |
| 8         | 30      | F   | 900                              | 400                         |
| 9         | 29      | M   | 800                              | 400                         |
| 10        | 33      | M   | 900                              | 200                         |
| 11        | 47      | M   | 900                              | 700                         |
| Mean dose |         |     | 854.5                            | 459.0                       |

Abbreviations: F = female, M = male.

improvement in affect, realizing that the core positive symptoms would not be likely to change, as there is no evidence that ziprasidone is superior to clozapine in the treatment of positive symptoms.

The strategy employed involved adding ziprasidone to the current clozapine regimen, with titration to a dose of ziprasidone, 160 mg/day. In most cases, ziprasidone was dosed once per day in the morning despite the half-life of 6.6 hours, as prior clinical experience showed this dosing schedule to be effective and it is conceptually supported by positron emission tomography binding data showing receptor occupancy for 18 to 24 hours.<sup>9,10</sup> After a patient reached stabilization on treatment with the medication, clozapine was tapered at a rate of 100 mg/month until the patient began to show symptoms of worsening of psychosis or reemergence of prior symptoms. On average, clozapine doses could be lowered 40% to 50% (Table 1).

Clinically, this regimen provided a significant benefit in terms of weight loss, improved initiation and motivation, reduced apathy, improved cognitive functioning, and improved lipid profiles in those patients for whom data were available. Improvement was judged by self-reports from the patient, at least 1 family member or significant other, and the clinician. All of the patients asked to stay on the combined regimen due to their own perceptions of the improvement gained by this augmentation strategy.

The ability to reduce the anticholinergic burden imposed by the use of clozapine and the positive benefits of ziprasidone's unique combined action of 5-HT<sub>1A</sub> agonism and 5-HT<sub>1D</sub> antagonism are presumed to underlie the positive changes observed. Ziprasidone is also known to block the reuptake of both serotonin and norepinephrine, and these mechanisms could also be contributory.<sup>5,6</sup>

No breakthrough in psychosis or exacerbation of original symptoms was observed. Further, there was no increase in side effects as reported by the patients both spontaneously and when directly queried by the psychiatrist. The potential of both compounds to increase QTc is a class effect. All of these patients had been on clozapine treatment in conjunction with at least 1 other antipsychotic in the past, and cardiac events had never been a clinical issue. While the package insert for ziprasidone<sup>5</sup> does caution about combining medications with similar potential effects on QTc, after approximately 1,000,000 prescriptions in the United States, there has been no confirmed case of torsade de pointes associated with ziprasidone (S. J. Romano, M.D.; Pfizer Pharmaceuticals, oral and electronic communication, December 2002).

This case series is limited by its open-label design. Ideally, placebo-controlled, randomized, double-blind, crossover design studies will be done in the future to expand on these clinical observations. However, due to the seriousness of schizophrenia as an illness and in consideration of the potential health risks of weight gain, especially in such a vulnerable patient population, concerned clinicians might consider using such rational poly-pharmacy as we strive to better treat some of medicine's most challenging patients.

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### Acute Liver Failure After Administration of the Herbal Tranquilizer Kava-Kava (*Piper methysticum*)

**Sir:** The chemistry and pharmacology of kava-kava (*Piper methysticum*) is unique among psycholeptic substances. The original kava drink is a suspension of lipid material in cold water used by native people for centuries and has not been linked with reports of liver failure. For commercial use, the lipid fraction is gained by alcoholic or acetonetic extraction from the root of the kava plant. The extract is dried and pressed into tablets. The major proportion of the lipid components of the kava pyrone consists of 6 chemically well-defined compounds containing the 4-methoxy-2-pyrone ring system (dihydrokavain, dihydromethysticin, kavain, methysticin, desmethoxyyangonin, and yangonin). The different kava pyrones have partially anxiolytic,<sup>1,2</sup> neuroleptic,<sup>3</sup> sedative-hypnotic, anticonvulsive,<sup>4</sup> muscle-relaxant, analgetic,<sup>5</sup> and spasmolytic effects. A cumulative action of kava combined with alcohol, barbiturates, psychotropics, and muscle relaxants resulting in coma has been described.<sup>6</sup> The exact knowledge of the psychopharmacology of kava is still incomplete.

**Case report.** We report the case of a 22-year-old woman who presented to her local physician with a 3-week history of nausea and fatigue and recently appeared jaundice. She had been in excellent health previously, had not been in contact with hepatitis or blood products, had not traveled abroad or drunk any alcohol, and reported no family history of liver disease. She had taken different ovulation inhibitors (norgestimate, 0.180 to 0.250 mg, and ethinyl estradiol, 0.035 mg) over a 1½-year period; twice a month, a 10-mg tablet of the pain reliever rizatriptan benzoate and acetaminophen (500 mg) for the treatment of migraine headache; and regularly, the herbal remedy kava-kava (240 mg of kava pyrone/day) for a period of 4 months before onset of symptoms. There was no foundation for a possible adverse herb-drug interaction in the patient's regimen before the kava was added. At the first visit to the doctor, her bilirubin level was 178 µmol/L and her alanine aminotransferase (ALAT) level was 519 IU/L (normal < 17 IU/L). The recommended admission was refused by the patient. One week later, she was admitted to the community hospital with further increase of her jaundice and beginning encephalopathy, grade I. The laboratory findings showed a beginning hepatic failure with a bilirubin level of 684 µmol/L, an ALAT level of 2442 IU/L, a γ-glutamyltransferase level of 61 IU/L, an alkaline phosphatase level of 246 IU/L, a cholinesterase level of 2474 IU/L, an activated partial thromboplastin time of 43 seconds, a thromboplastin time of < 20% (prothrombin time expressed in % of normal, international normal ratio 7.3), and an ammonia level of 123 µg/dL. As the encephalopathy and hepatic failure increased in the course of time, the patient was transferred to the university hospital within the next 3 days. On examination, she was icteric, afebrile, and comatose grade II and had no signs of chronic liver disease or hepatosplenomegaly. The laboratory findings were as follows: bilirubin level, 487 µmol/L; ALAT level, 453 IU/L; alkaline phosphatase level, 287 IU/L (normal is 60–180 IU/L); activated partial thromboplastin time, 69 seconds; thromboplastin time, < 10% (prothrombin time expressed in % of normal, international normal ratio 7.3); ceruloplasmin, 17 mg/dL (20–60 mg/dL); copper, 79 µg/L; platelets, 199,000 g/L; and ammonia (plasma), 87 µg/dL. Results of viral serological tests (hepatitis A, B, and C; herpes simplex virus; and cytomegalovirus [CMV]) and complete toxicological screening of the urine were negative. The serum concentrations of the immunoglobulins IgG, IgA, and IgM were within normal limits. Ultrasonography showed no hepatic or biliary abnormalities. Due to the increasing hepatic failure, she was listed "high urgency" on the eurotransplant liver waiting list on the day of admission. The next day, she became further comatose (grade III–IV) with an ammonia level of 163 µg/dL. An albumin dialysis was performed to reduce ammonia in plasma, which significantly improved the vigilance of the patient for several hours. While waiting for the availability of an organ, the patient had an intracranial pressure probe implanted. Within the next hours, the cerebral and pulmonary function of the patient deteriorated further.

On the third day, an organ became available and orthotopic liver transplantation, in standard technique, was performed. The histological examination of the failed liver revealed a reduced size of the liver (780 g) and massive subacute hepatic necrosis with nearly complete destruction of the parenchyma. Extensive lobular and intermediate necrotic areas and focally proliferating small bile ducts along the portal tracts were seen. Only occasional hepatocytes, which were hydropic and necrobiotic, were recognizable on the HE-stained section. No signs of portal fibroplasia, cirrhotic reconstruction, an acute hepatitis, or copper storage disease were found. The recovery of the patient during the next 12 weeks was complicated by 2 recurrent CMV infections and continuous jaundice with a bilirubin level of 220 µmol/L and an ALAT level of 100 to 115 IU/L. Immunosuppres-

sion was maintained with oral FK506 (3 mg/day) and corticosteroid (8 mg/day). She was released from the hospital in good physical constitution 12 weeks after transplantation. Several months later, after rehabilitation, she had to be admitted again because of multiple pulmonary and cerebral aspergilloma. Despite maximal antifungal therapy, she died 6 months after liver transplantation in aspergillin sepsis.

The hepatotoxicity of the herbal remedy kava-kava (*Piper methysticum*) was discussed recently, because of several international reports to European regulatory authorities ranging from temporary jaundice and increase of transaminases up to histologically verified hepatic necrosis and 4 cases with fulminant hepatic failure followed by liver transplantation.<sup>7–9</sup> Most patients were between 20 and 60 years old and became symptomatic after regular intake of a daily dose of 120 to 240 mg of kava pyrone over a period of 4 to 16 weeks. The mechanism of this side effect is not known. Obviously, there is no difference in the hepatotoxicity of the different preparations, because fulminant hepatic failure occurred after the intake of the acetonic as well as the alcoholic kava extract.<sup>7–9</sup> It is also not known if the kava pyrone itself or other ingredients of the kava extract were responsible for the described hepatotoxic side effects. Previous data suggest that the hepatotoxic activity is due to a toxic drug reaction or due to an immunoallergic mechanism in the kava-kava-associated hepatic failure.

A causal connection between the intake of the herbal medicine kava-kava and our patient's acute, fulminant hepatic failure is supported by the exclusion of viral, autoimmune, copper storage, and biliary diseases, as well as by the time link between administration of kava-kava and onset of the liver failure. Like all other reported cases about hepatotoxic effects of kava pyrone, the first symptoms occurred within 16 weeks of intake of 240-mg daily doses. The additional concomitant medications consisted of the continuous intake of an ovulation inhibitor over a period of 1½ years that was well tolerated and the occasional intake of the antimigraine pain relievers acetaminophen and rizatriptan benzoate. It is very unlikely that one of these additional medications was responsible for the hepatotoxic effect, as only reversible cholestasis and no hepatotoxic effects have been reported for ovulation inhibitors. Acetaminophen, indeed, can cause hepatic damage, but only after ingestion of well-known toxic doses (> 7500 mg), in a dose-dependent manner. Several grams of acetaminophen intake at one time are needed to cause hepatic damage, and our patient took 500 mg, about twice a month, as an occasional pain reliever.

Because of this case and the recent accumulation of acute liver failure after kava-kava ingestion in Switzerland and Germany, the pharmaceutical licensure for kava-kava and kavain-containing herbal remedies was under investigation. On June 14, 2002, the licensures for kava-kava (*Piper methysticum*) and kavain-containing herbal remedies with concentrations greater than D4 were withdrawn in Germany. Although acute hepatic failure after intake of alcoholic or acetonic kava-kava extracts was only reported from Switzerland and Germany, the authors suppose that the kava-kava-associated liver damage is potentially a worldwide problem and not limited to specific manufacturers or distributors.

*The authors report no financial or other relationship relevant to the subject matter of this letter.*

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### Priapism Associated With Risperidone: A Case Report

**Sir:** We treated a patient who developed priapism during therapy with risperidone and divalproex sodium. He required emergent urologic surgery. Physicians are reminded of the risk and potential consequences of priapism associated with atypical antipsychotic agents.

**Case report.** Mr. A, a 26-year-old Hispanic man with a 2-year history of intermittent mood and psychotic symptoms diagnosed as bipolar disorder (DSM-IV criteria), had a 5-day history of persistent erection, dysuria, and urinary incontinence. He had had no prior similar episodes. His only medications were risperidone, 3 mg/day, and divalproex sodium, 1500 mg/day, which he had been receiving for 1 year; 3 mg/day had been his maximum risperidone dose. Mr. A had previously taken haloperidol (dose unknown) and had never received trazodone. He occasionally used marijuana and alcohol. His medical history was unremarkable for illnesses associated with priapism. The patient's affect was dysphoric and restricted, his speech was slow, and he had neither violent ideations nor psychosis. He had a hematocrit of 35% and white blood cell and platelet counts within normal limits. Toxicology revealed no marijuana, cocaine, or amphetamines.

Mr. A's erection persisted despite 2 corpora cavernosa irrigations with phenylephrine. Corpora cavernosa venous blood gas analysis revealed pH of 6.92, pO<sub>2</sub> of 4, and pCO<sub>2</sub> of 91, consistent with the hypoxia and acidosis of low-flow priapism.<sup>1</sup> A Winters shunt (cavernosal glandular shunt) and a corpora cavernosum/corpus spongiosum shunt were performed.<sup>2</sup> Due to his prolonged priapism with resultant penile fibrosis, Mr. A was

advised of a 90% risk of permanent erectile dysfunction. Risperidone was discontinued, and olanzapine, 10 mg q.h.s., and paroxetine, 20 mg/day, were added. The patient was discharged on the second postoperative day. At a urology clinic follow-up 10 weeks later, he had not been able to achieve an erection since his hospitalization.

Priapism is a prolonged, usually painful, and persistent erection not associated with sexual stimulation.<sup>1</sup> Nonpsychopharmacologic causes of priapism include some antihypertensives, anticoagulants, alcohol, marijuana, cocaine, hematologic disorders (sickle cell anemia, leukemia, lymphoma, thrombocytopenia), and perineal trauma.<sup>1</sup> An estimated 50% of drug-induced priapism cases occur with psychotropics.<sup>3</sup> Psychotropic-induced cases relate to the  $\alpha$ -adrenergic effects of psychotropics, in which pharmacologic blockade in the corpora cavernosa inhibits sympathetic-mediated detumescence.<sup>1,3</sup> This "low-flow" or "veno-occlusive" priapism leads to venous stasis, hypoxia, ischemia, and acidosis and can result in irreversible cavernosal fibrosis.<sup>1,3,4</sup> Management includes intracavernous injection of an  $\alpha$ -adrenergic agonist.<sup>1</sup> Surgery may be necessary to establish a shunt between the corpora cavernosa and corpus spongiosum.<sup>2,3</sup> Post-priapism impotence is seen in up to 50% of cases.<sup>1,3</sup>

Priapism may occur at any time during the course of psychotropic therapy and may occur without a change in dose.<sup>3</sup> Priapism has been associated with trazodone, phenelzine, methaqualone, buspirone, hydroxyzine, and typical antipsychotics.<sup>1,3,5,6</sup> Among the atypical antipsychotics, cases of prolonged erection or priapism have been associated with clozapine, risperidone, and olanzapine.<sup>2,4,6-16</sup> To date, no cases have been reported with quetiapine or ziprasidone.<sup>1</sup>

It is unlikely that divalproex sodium was involved in our patient's priapism, as it does not have  $\alpha$ -adrenergic blocking properties and does not interact problematically with risperidone. A PubMed search of articles published in English from 1966 to 2002, using the keywords *divalproex sodium and priapism*, *valproic acid and priapism*, and *valproate and priapism*, revealed no cases of priapism attributed to divalproex sodium.

Our patient had none of the systemic illnesses associated with priapism, although it is possible that his marijuana and alcohol use may have contributed to the onset of the episode of priapism, perhaps acting in "synergy" with his risperidone treatment. Physicians prescribing atypical antipsychotics should be aware of the possibility that this rare but potentially serious adverse event can occur at any time during antipsychotic treatment, especially in a patient with a history of priapism associated with other psychotropics.<sup>7</sup>

*The authors report no financial affiliation or other relationship relevant to the subject matter of this letter.*

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### Clozapine-Induced Rabbit Syndrome

**Sir:** The rabbit syndrome is a distinct antipsychotic-induced extrapyramidal syndrome, described by Villeneuve as the rapid, rhythmic involuntary movements of the oral and masticatory muscles except for the tongue, with a frequency of about 5.0 Hz.<sup>1</sup> It is often misdiagnosed as tardive dyskinesia because it appears late in antipsychotic therapy and involves the buccal-masticatory muscle group.

**Case report.** Ms. A, a 48-year-old woman, diagnosed according to DSM-IV with schizophrenia and treated for more than 2 years with various antipsychotics, presented with fine movements involving the jaw. The patient had no history of other psychiatric disorder. Initial treatment with chlorpromazine, haloperidol, and depot long-acting neuroleptic (fluphenazine decanoate) either as monotherapy or in combination for about 2 years did not relieve the symptoms, and the patient developed involuntary dyskinetic movements of tongue, both hands, and feet. At this time, a trial with risperidone was started since this drug is less likely to cause tardive dyskinesia. However, the dyskinetic movements persisted, and Ms. A relapsed. Treatment with clozapine was started. The tardive dyskinetic movements worsened initially during the washout period but gradually resolved completely. Seven months later (at a clozapine dose of 225 mg/day), involuntary movements of the jaw were noticed that were fine, rapid, and rhythmic and were along a vertical axis. These movements spared the tongue. No other side effects were noticed. Diagnosis of rabbit syndrome was made, and trihexyphenidyl, 4 mg/day, was prescribed. Within 10 days of treatment with trihexyphenidyl, these movements resolved completely. The patient continues to do well on clozapine (225 mg/day), and trihexyphenidyl was gradually withdrawn without reappearance of any side effects.

The rabbit syndrome is long-term complication of high-potency typical antipsychotics.<sup>2</sup> The incidence of rabbit syn-

drome is considered to be low with atypical antipsychotics. Schwartz et al.,<sup>3</sup> however, reported a case of rabbit syndrome with risperidone. A manual and computer search has not revealed any case of rabbit syndrome induced by clozapine.

The rabbit syndrome is considered to be a form of antipsychotic-induced extrapyramidal syndrome (EPS),<sup>4,5</sup> but it differs from classical EPS in that it appears late in treatment and may appear in the absence of other extrapyramidal side effects. The picture is similar in our case. The fact that the rabbit syndrome could be induced with atypical antipsychotics and that it responds well to anticholinergic treatment poses a question whether it is mediated through a different neuronal pathway. Also, clozapine itself is credited with high anticholinergic properties, but our patient required additional anticholinergic treatment for the symptom control.

Both tardive dyskinesia and rabbit syndrome are sequelae of long-term antipsychotic treatment, but the 2 can be easily differentiated.<sup>6</sup> The orofacial involvement in tardive dyskinesia is manifested by chewing-like movements including writhing or thrusting tongue movements. Also, the movements in tardive dyskinesia are slower and less regular than the ones seen in rabbit syndrome. Further, the differentiation of rabbit syndrome from tardive dyskinesia is important from the management point as the former responds favorably to treatment with anticholinergics.<sup>4</sup>

*The authors report no financial or other relationships relevant to the subject matter of this letter.*

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### AMPA Blockade May Be the Mechanism Underlying the Efficacy of Topiramate in PTSD

**Sir:** We read with great interest the report of Berlant and van Kammen<sup>1</sup> on topiramate in posttraumatic stress disorder (PTSD). They report particularly on suppression of nightmares and flashbacks and propose the suppression of kindling mechanisms as underlying topiramate's efficacy for these symptoms. We would propose a further possible mechanism, which has not been considered by the authors.

Important data show the role of glutamatergic mechanisms in synaptic plasticity and long-term behavioral adaptations. Experiments on behavioral sensitization indicate that whereas *N*-methyl-D-aspartate (NMDA) receptors are involved in induc-

tion,<sup>2</sup>  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors may mediate expression of the established response.<sup>3</sup> As Berlant and van Kammen state, topiramate acts, among other pathways, through inhibition of glutamatergic AMPA receptors.

Blocking, or at least modulating, hippocampal AMPA receptors can be hypothesized to be a possible mechanism augmenting the threshold of flashback activations, after sensitization has already occurred. The effect will therefore be coupled not to a reduction of kindling, but to suppression of the activation of kindled processes. Furthermore, AMPA receptors may play an important role in the activation of the locus ceruleus by glutamate.<sup>4</sup> Hyperreactivity of the locus ceruleus has previously been suggested to be involved in some anxiety phenomena.<sup>5</sup>

In conclusion, together with the antkindling properties shared with other anticonvulsants, topiramate is, due to its AMPA-blocking properties, an especially interesting drug for disorders characterized by reactivation of maladaptive memory mechanisms. Besides treating PTSD, topiramate may be valuable in treating other anxiety disorders, such as panic disorder, but also substance abuse disorders.

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