


Preventative effects of aripiprazole and quetiapine on seizure and lethality in a mice cocaine toxicity model: an experimental study

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Abstract

Objective: To assess the effectiveness of pre-treatment with aripiprazole and quetiapine to prevent acute cocaine toxicity in a mouse model of cocaine toxicity.

Methods: This experimental study included three groups ($n = 25$ per group) of mice that were intraperitoneally injected with normal saline solution, 10 mg/kg quetiapine or 10 mg/kg aripiprazole 15 min before 105 mg/kg cocaine hydrochloride. When the cocaine administration was completed, researchers blinded to the study groups observed the mice in terms of seizures and death for a further 30 min.

Results: In the cocaine + quetiapine group, the mean \pm SE time to the first seizure was 10.80 \pm 2.27 min and seizure activity was detected in 18 mice (72%) by the end of the 30 min. In the cocaine + aripiprazole group, the mean \pm SE time to the first seizure was 18.10 \pm 1.94 min and seizure activity was detected in 15 mice (60%) by the end of the 30 min. When compared with the control group, there was a significant difference between the cocaine + quetiapine and cocaine + aripiprazole groups in terms of seizure activity. Survival time was increased in the cocaine + aripiprazole group compared with the control and cocaine + quetiapine groups.

Conclusion: Quetiapine and aripiprazole pre-treatment reduced seizure activity and delayed the onset of seizures compared with the control group.

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Introduction

Cocaine is responsible for 505 224 visits to emergency departments in the United States.¹ In addition to being the cause of acute and chronic toxicity, cocaine is also one of the most common causes of drug-related deaths.² In the United Kingdom in 2010–2011, 2047 people received inpatient treatment due to cocaine poisoning.³ According to the US National Institute on Drug Abuse, approximately 7000 deaths due to cocaine overdose occurred in the US in 2015.²

Cocaine leads to repetitive activation of postsynaptic alpha-beta adrenergic, serotonergic, and dopaminergic neurons by inhibiting the carrier protein responsible for epinephrine, norepinephrine, serotonin and dopamine re-uptake into presynaptic neurons.⁴ At toxic doses of cocaine, the motor centres in the medulla spinalis are stimulated and the seizure threshold falls, leading to tonic–clonic seizures.⁵ Seizures linked with cocaine have been associated with morbidity and mortality in cocaine toxicity.⁶ Seizures and status epilepticus are among the neurological complications of cocaine overdose in human beings.⁷ Research has suggested that serotonin is significantly involved in the formation of cocaine-induced convulsions.⁸

The new generation of atypical antipsychotic drugs have recently been used for the emergency treatment of acute psychosis.⁹ Aripiprazole and quetiapine, new generation antipsychotic agents, have antagonist effects on dopaminergic receptors as well as on serotonergic receptors.^{10,11}

The clinical effect of dopamine and serotonergic system antagonism, which is effective in acute cocaine toxicity, is not fully understood. Antipsychotic treatment has been shown to reduce the risk of death by 27% compared with placebo in animal models.⁶

This study aimed to determine the efficacy of aripiprazole and quetiapine, which to the best of our knowledge have not previously been studied, to prevent seizures and deaths in mice due to cocaine intoxication.

Materials and methods**Study design**

This experimental study was undertaken in the Pamukkale University Experimental Surgical Application and Research Centre Laboratory, Pamukkale University of Medical Sciences, Denizli, Turkey in October 2017. In order to reduce the impact of circadian rhythms on the threshold for convulsions, all experiments were performed during 14:00–18:00. Experimental protocols followed the Guidelines of the US National Institutes of Health with regard to the care and use of animals for research purposes, the European Communities Council Directive of 24 November 1986 (86/609/EEC) and the Animal Ethics Committee of Pamukkale University Faculty of Medicine (no. PAUHDEK-2015/15).

Seventy-five male, 12-week old Balb/c mice weighing 35–40 g were obtained from Pamukkale University Experimental Surgical Application and Research Centre

(Denizli, Turkey). The mice were housed in separate cages, maintained at 21°C under a 12-h light/12-h dark cycle with free access to water and pelleted food. The mice were randomly divided into three groups (quetiapine, aripiprazole and saline control; $n = 25$ per group) according to a computer-generated randomization schedule. The researcher (A.Y.) carried out the investigation without knowing the treatment groups throughout the entire study.

Study groups and interventions

The three groups of mice were pre-treated as follows: (i) group 1, 0.5 ml 0.9% saline (control); (ii) group 2, 10 mg/kg quetiapine (Astra Zeneca Pharmaceuticals, Wilmington, DE, USA); and (iii) group 3, 10 mg/kg aripiprazole (Otsuka Pharmaceutical Laboratories Europe, London, UK). The doses of quetiapine and aripiprazole used in the current study were in line with the drug doses used in previous studies.^{12–15} Drugs in all study groups were administered as a pre-treatment before the cocaine treatment. All groups were administered 105 mg/kg cocaine hydrochloride (HCl) via an intraperitoneal injection (dose was 70% of the lethal dose) 15 min after the pre-treatment drug administration.^{16,17} Cocaine HCl was obtained from Lipomed Laboratories (Arlesheim, Switzerland).

Drug administration and procedures

All of the injections were administered intraperitoneally using a 25 G syringe. Intraperitoneal administration was chosen because it is the standard method in rodent cocaine toxicity models.¹⁸ Cocaine HCl was diluted with sterile distilled water to obtain a 6.3 mg/dl cocaine HCl solution. Aripiprazole was diluted with dimethyl sulfoxide to obtain a 10 mg/kg aripiprazole solution.¹³ Quetiapine was diluted with 0.9% saline to obtain a 10 mg/kg quetiapine

solution. The mice were injected with all of the aforementioned drugs intraperitoneally 15 min before the administration of 105 mg/kg cocaine HCl.

Main outcome measures

The mice were placed in separate observation cages from the beginning of the study. The preliminary findings in this study were seizure activity and lethality. Seizures were defined as convulsions whose indications included righting reflex, tonic-clonic activity or popcorn jumping.¹⁶ Lethality was characterized by the emergence of agonal respiration, seizures enduring over 8.5 min or failure to ambulate until 30 min following the cocaine administration.¹⁹ The lethality and seizures were assessed in an observational way. The changes in mice during the 30-min observation period were recorded on observational scales previously prepared for each group separately.

The secondary findings were observed at the end of this study when the ratio of seizure frequency and the time until the first seizure were determined. All findings were logged by blinded researchers (A.Y., R.S. and A.S.) who monitored the mice over 30 min. All of the mice in the study were sacrificed when the experiment came to an end at the 30th min.

Statistical analyses

In light of previous research,²⁰ a power calculation estimated that 80% power could be obtained at a 95% confidence level if at least 23 mice were included in each group, assuming that the effect size would be obtained from the study ($w = 0.4$).

All statistical analyses were performed using the SPSS[®] statistical package, version 17.0 (SPSS Inc., Chicago, IL, USA) for Windows[®]. The Kaplan–Meier model was used to undertake the survival analysis. χ^2 -test and Fisher's Exact test were used to

compare qualitative data. Log-Rank test was used for analysing times to first seizure and death. P -values < 0.05 were considered significant in the Log-Rank test. The Bonferroni correction was used in the Log-Rank test for *post-hoc* comparisons when the Log-rank test was found to be significant. P -values < 0.017 were considered significant in the Bonferroni correction. For all other tests, a P -value < 0.05 was considered statistically significant.

Results

The seizure and mortality rates in the three study groups are presented in Table 1. Significant sedation was initially observed in the two drug groups (quetiapine and

aripiprazole) after intraperitoneal injection. There was a significant difference between the cocaine + quetiapine and cocaine + aripiprazole groups compared with the control group in terms of seizure activity ($P < 0.001$ for both comparisons). There was no significant difference between the cocaine + quetiapine and cocaine + aripiprazole groups compared with the control group in terms of mortality rates.

When the control group was assessed for seizure activity, the mean \pm SE time to first seizure was 2.48 ± 0.21 min (95% confidence interval [CI], 2.05, 2.90) (Table 2) and seizures were detected in all 25 mice (100%) in this group by the end of 4 min. In the cocaine + quetiapine group, the mean \pm SE time to first seizure

Table 1. Seizure and mortality rates triggered by cocaine in a mouse model of cocaine toxicity.

| Variable | Study groups | | | Total | Statistical significance ^b |
|----------|------------------|----------------------|-------------------------------------|-----------|---------------------------------------|
| | Cocaine + saline | Cocaine + quetiapine | Cocaine + aripiprazole ^a | | |
| Seizure | 25 (100) | 18 (72.0) | 15 (60.0) | 58 (77.3) | $P < 0.001$ |
| Death | 18 (72.0) | 19 (76.0) | 19 (76.0) | 56 (74.7) | NS |

Data presented as n of mice (%).

^a $P < 0.001$ for cocaine + aripiprazole versus cocaine + quetiapine; Fisher's Exact test.

^b χ^2 -test; NS, no significant between-group difference ($P \geq 0.05$).

Table 2. Seizure and mortality times triggered by cocaine in a mouse model of cocaine toxicity.

| Study group | Time, min | 95% confidence interval | Statistical significance |
|------------------------|------------------|-------------------------|--------------------------|
| Seizure time | | | |
| Cocaine + saline | 2.48 ± 0.21 | 2.05, 2.90 | |
| Cocaine + quetiapine | 10.80 ± 2.27 | 6.35, 15.25 | $P < 0.017^a$ |
| Cocaine + aripiprazole | 18.10 ± 1.98 | 14.30, 21.90 | $P < 0.017^a$ |
| Mortality time | | | |
| Cocaine + saline | 14.20 ± 1.99 | 10.28, 18.11 | |
| Cocaine + quetiapine | 12.60 ± 2.00 | 8.67, 16.52 | |
| Cocaine + aripiprazole | 20.20 ± 1.33 | 17.59, 22.80 | NS ^b |

Data presented as mean \pm SE.

^aLog-Rank test with Bonferroni correction.

^bLog-Rank test; NS, no significant between-group difference ($P \geq 0.05$).

was 10.80 ± 2.27 min (95% CI, 6.35, 15.25) and seizures were detected in 18 mice (72%) by the end of 30 min. In the cocaine + aripiprazole group, the mean \pm SE time to seizure was 18.10 ± 1.94 min (95% CI, 14.30, 21.90) and seizures were detected in 15 mice (60%) by the end of 30 min. There was a significant difference between the cocaine + quetiapine and cocaine + aripiprazole groups when the time to first seizure for these two groups were compared with the control group (cocaine + saline) ($P < 0.017$ for both comparisons) (Figure 1). There was also a significant difference between cocaine + quetiapine and cocaine + aripiprazole groups when these groups were compared in terms of time to first seizure ($P < 0.017$).

When the control group was evaluated for death, the mean \pm SE time to death was 14.20 ± 1.99 min (95% CI, 10.28, 18.11) (Table 2) and death occurred in 18 mice (72%) by the end of 30 min (Figure 2). In the cocaine + quetiapine group, the mean \pm SE time to death was

12.60 ± 2.00 min (95% CI, 8.67, 16.52) and death occurred in 19 mice (76%) by the end of 30 min. In the cocaine + aripiprazole group, the mean \pm SE time to death was 20.20 ± 1.33 min (95% CI, 17.59, 22.80) and death occurred in 19 mice (76%) by the end of 30 min. Although there was no significant difference between the three the groups in terms of the time to death, the cocaine + aripiprazole group had a longer survival time to death compared with the other two groups based on the Kaplan–Meier survival curve analysis (Figure 2).

Discussion

This current study demonstrated that quetiapine and aripiprazole pre-treatment reduced the seizure activity and prolonged the time to first seizure compared with the control group in an animal model of acute cocaine toxicity. In addition, the current study also found that the mortality rate was not significantly different between the three groups, but the time to death was

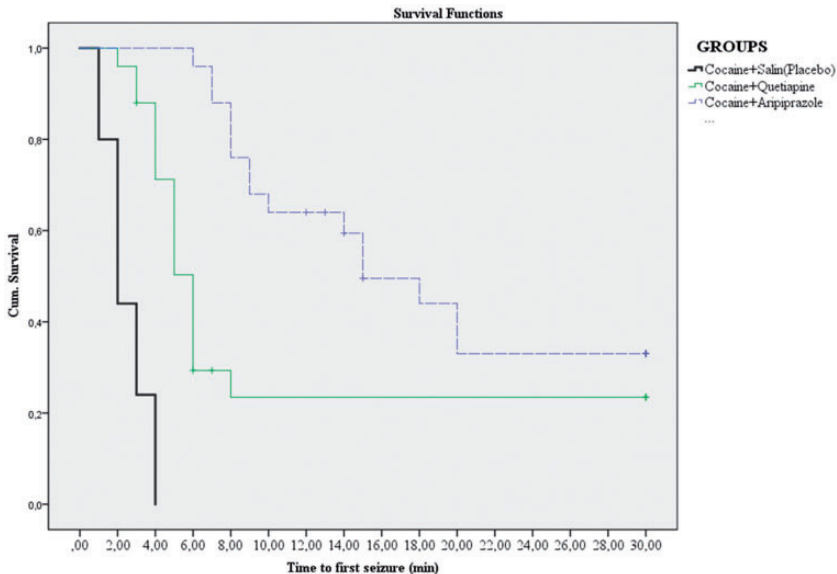


Figure 1. Kaplan–Meier survival curve analyses for time to seizure triggered by cocaine in a mouse model of cocaine toxicity. The colour version of this figure is available at: <http://imr.sagepub.com>.

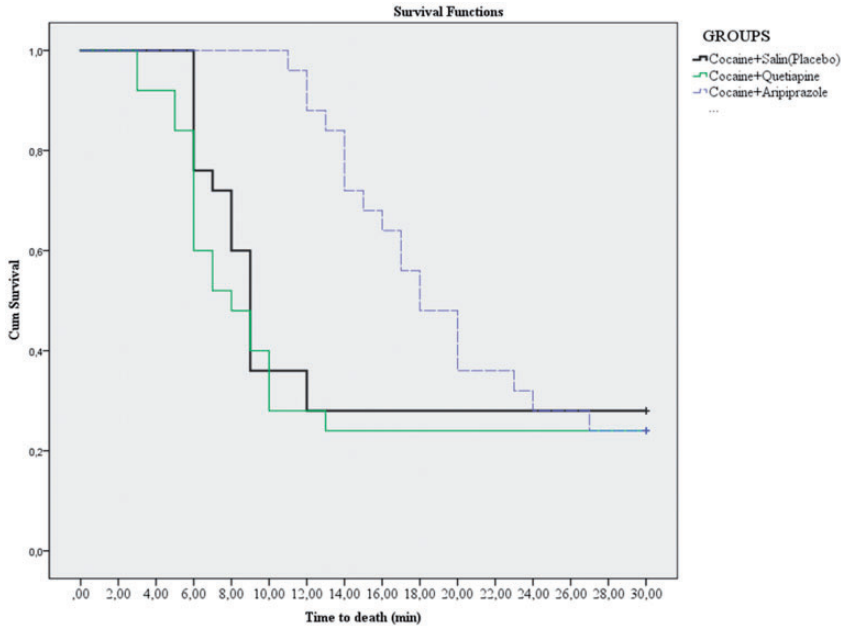


Figure 2. Kaplan–Meier survival curve analyses for time to death triggered by cocaine in a mouse model of cocaine toxicity. The colour version of this figure is available at: <http://imr.sagepub.com>.

increased in the cocaine + aripiprazole group. To the best of our knowledge, this is the first study of the effects of quetiapine and aripiprazole pre-treatment on acute cocaine toxicity in a mouse model. A review of the published literature shows that benzodiazepines and GABAergic drugs have been studied previously in an acute cocaine intoxication model.^{6,19} Ziprasidone, an atypical antipsychotic agent, has been used as a pre-treatment in several studies evaluating cocaine-induced seizures and death.^{16–18} A review of the published literature did not identify any cocaine toxicity studies that investigated the new generation antipsychotic agents except ziprasidone; and none appear to have investigated quetiapine and aripiprazole in cocaine toxicity.

The seizures caused by cocaine have been associated with the induction of dopamine-1 (D1) receptors, so cocaine-related mortality can be minimized through D1 receptor

antagonists.²¹ First-generation antipsychotic drugs are known to lower the seizure threshold.^{22,23} Regarding the new generation antipsychotics, the issue of whether they are safer than first-generation antipsychotics in terms of seizure induction is unclear because of the severe lack of data.^{24–26} There has been research into the effect of quetiapine on seizures, but this focussed on seizures seen in a patient receiving stable doses of long-term quetiapine.²⁷ It has been established that 0.1% of schizophrenia and 0.3% of bipolar manic patients treated with aripiprazole had undergone seizures.^{28,29} Electroencephalogram abnormalities have been reported to occur with both typical and atypical antipsychotic use.³⁰ Another study reported that second-generation antipsychotic drugs have a higher risk of seizure activity than first-generation antipsychotics.²⁴ Ziprasidone, a new generation antipsychotic drug, was not effective in preventing seizures in an animal

model of acute cocaine toxicity, but it was stated that ziprasidone would be effective in preventing seizures at the lower doses of cocaine.^{16,18} Diazepam and Albu-CocH1 protein inhibited cocaine-induced seizures in a rats model of cocaine toxicity.³¹

In this current study, 77.3% of all of the study animals had a seizure in response to cocaine treatment. Quetiapine and aripiprazole pre-treatment not only significantly reduced the incidence of seizures but also significantly prolonged the time to onset of the first seizure compared with the control group. The current study also found a significant difference in the time to the first seizure between the cocaine + quetiapine and cocaine + aripiprazole groups. Aripiprazole, unlike other atypical antipsychotics, is a D2 and serotonin (5HT) 1A receptor partial agonist.^{30,32} Like other atypical antipsychotics, aripiprazole is a high affinity antagonist at 5HT2A receptors and a moderate affinity antagonist at histamine and α -adrenergic receptors.³³ In contrast, quetiapine is a multiple receptor antagonist with low D2 receptor affinity and high 5HT2A, 5HT1A, α -1 and α -2 adrenergic and histamine H1 receptor affinities.³⁴

Cocaine accelerates the activity of monoamine neurotransmitters by blocking dopamine, norepinephrine and serotonin re-uptake pumps in the central and peripheral nervous system,³⁵ through which cardiovascular complications, seizures and deaths occur. Drugs that are antagonists for dopaminergic, serotonergic and muscarinic cholinergic receptors have the potential to reduce cocaine-related toxicity.²¹ Considering these various neurotransmitter interactions, the current study postulated that the differences in the duration of seizure prevention and the rate of seizures between the cocaine + aripiprazole and cocaine + quetiapine groups were probably due to differences in D2 and 5HT1-A receptor affinities.

In this current study, quetiapine and aripiprazole did not significantly reduce mortality due to cocaine toxicity. In addition, the time to death was not significantly different when the cocaine + aripiprazole group was compared with the cocaine + quetiapine and control groups, but the cocaine + aripiprazole group had a longer survival time to death according to the Kaplan–Meier survival analysis. Cocaine boosts dopamine release in many regions of the brain, and SCH 23390, a selective D1 dopamine receptor antagonist, reduces mortality in acute cocaine intoxication.³⁶ However, haloperidol, a widely used dopamine antagonist, is considered ineffective in reducing cocaine-induced mortality.³⁷ However, these studies may fall short of providing insightful results into the cocaine intoxication phenomenon. Haloperidol has been reported to produce little effect on serotonin receptors and has been proven to be ineffective for cocaine poisoning.²⁴ In contrast, aripiprazole is a drug that has a high degree of antagonism for 5HT-2 serotonin and dopamine receptors, which is a possible explanation for why it prolongs the time to death in acute cocaine toxicity as observed in this current animal study.

Ziprasidone, which is an antagonist at the 5HT-2 receptor, has been shown to reduce cocaine-induced mortality.¹⁶ The doses of aripiprazole and quetiapine used in this current might not have been sufficient to reduce the death rate of the cocaine-treated mice. Furthermore, in cocaine toxicity, death is not only caused by central nervous system effects but also by cardiovascular system effects.³⁸ Since the effects on the cardiovascular system were not assessed in this current study, the number of seizure-independent deaths remains unknown, which may have caused the incidence of death to remain unchanged between the three groups. More promising drugs, such as cocaine hydrolases, have been used for cocaine-induced mortality

and they have been shown to be effective in rats.³¹

This current study had several limitations. First, it was undertaken as a pre-treatment study because this is the appropriate method to use when the average time of death of the mice in response to cocaine toxicity is taken into account. However, this is not how people who are admitted to the emergency department with cocaine toxicity would be treated. Secondly, the study used an animal model of cocaine toxicity, which may not be applicable to humans. Thirdly, the study did not measure the effects of cocaine, quetiapine and aripiprazole on dependent variables, such as heart rate, blood pressure, body temperature, cardiac rhythm and electroencephalography. Similarly, non-convulsant seizures and cardiac-induced deaths in response to cocaine toxicity were not measured.

In conclusion, an acute cocaine toxicity model in mice showed that pre-treatment with quetiapine and aripiprazole reduced the incidence of seizures and prolonged the time to first seizure. The time to death was prolonged in the group pre-treated with aripiprazole, but neither of the drugs protected the mice from cocaine-induced death. These findings support previous findings that serotonin and dopamine are contributing to the toxic effects of cocaine. More studies on the protective effects of atypical antipsychotics and new promising drugs such as cocaine hydrolases in cocaine toxicity are required.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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References

1. Crane EH. Highlights of the 2011 Drug Abuse Warning network (DAWN) Findings on Drug- Related Emergency Department Visits. The CBHSQ Report: February 22, 2013. Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration, Rockville, MD.
2. National Institute on Drug Abuse. Overdose Death Rates, <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates/> (2017, accessed 18 October 2018).
3. European Monitoring Centre for Drugs and Drug Addiction. Emergency health consequences of cocaine use in Europe, http://www.emcdda.europa.eu/system/files/publications/778/Cocaine_emergencies_report_final_467089.pdf_en/ (2014, accessed 18 October 2018).
4. Sharma HS, Muresanu D, Sharma A, et al. Cocaine-induced breakdown of the blood-brain barrier and neurotoxicity. *Int Rev Neurobiol* 2009; 88: 297–334.
5. Tseng CC, Derlet RW and Albertson TE. Acute cocaine toxicity: the effect of agents in non-seizure-induced death. *Pharmacol Biochem Behav* 1993; 46: 61–65.
6. Heard K, Cleveland NR and Krier S. Benzodiazepines and antipsychotic medications for treatment of acute cocaine toxicity in animal models – A systematic review and meta-analysis. *Hum Exp Toxicol* 2011; 30: 1849–1854.
7. McCarron MM and Wood JD. The cocaine 'body packer' syndrome. Diagnosis and treatment. *JAMA* 1983; 250: 1417–1420.
8. O'Dell LE, Kreifeldt MJ, George FR, et al. The role of serotonin (2) receptors in mediating cocaine-induced convulsions. *Pharmacol Biochem Behav* 2000; 65: 677–681.
9. Thomas P, Alptekin K, Gheorghe M, et al. Management of patients presenting with

- acute psychotic episodes of schizophrenia. *CNS Drugs* 2009; 23: 193–212.
10. de Bartolomeis A, Tomasetti C and Iasevoli F. Update on the Mechanism of Action of Aripiprazole: Translational Insights into Antipsychotic Strategies Beyond Dopamine Receptor Antagonism. *CNS Drugs* 2015; 29: 773–799.
 11. Meltzer HY, Li Z, Kaneda Y, et al. Serotonin receptors: their key role in drugs to treat schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; 27: 1159–1172.
 12. Natesan S, Reckless GE, Barlow KB, et al. Partial agonists in schizophrenia – why some work and others do not: insights from preclinical animal models. *Int J Neuropsychopharmacol* 2011; 14: 1165–1178.
 13. Kim YR, Kim HN, Hong KW, et al. Antidepressant effects of aripiprazole augmentation for cilstazol-treated mice exposed to chronic mild stress after ischemic stroke. *Int J Mol Sci* 2017; 18: E355.
 14. Porter JH and Prus AJ. Discriminative stimulus properties of atypical and typical antipsychotic drugs: a review of preclinical studies. *Psychopharmacology (Berl)* 2009; 203: 279–294.
 15. Bi X, Yan B, Fang S, et al. Quetiapine regulates neurogenesis in ischemic mice by inhibiting NF-kappaB p65/p50 expression. *Neurol Res* 2009; 31: 159–166.
 16. Cleveland NJ, DeWitt CD and Heard K. Ziprasidone pretreatment attenuates the lethal effects of cocaine in a mouse model. *Acad Emerg Med* 2005; 12: 385–388.
 17. Yuksel A, Erdur B, Kortunay S, et al. Assessment of propofol, midazolam and ziprasidone, or the combinations for the prevention of acute cocaine toxicity in a mouse model. *Environ Toxicol Pharmacol* 2013; 35: 61–66.
 18. Cleveland NR, Krier S and Heard K. Ziprasidone, diazepam, or the combination for prevention of cocaine toxicity in a mouse model. *Acad Emerg Med* 2007; 14: 691–694.
 19. Erdur B, Degirmenci E, Kortunay S, et al. Effects of pretreatment with etomidate, ketamine, phenytoin, and phenytoin/midazolam on acute, lethal cocaine toxicity. *Neurol Res* 2012; 34: 952–956.
 20. Seyit M, Erdur B, Kortunay S, et al. A comparison of dexmedetomidine, moxonidine and alpha-methyl-dopa effects on acute, lethal cocaine toxicity. *Iran Red Crescent Med J* 2015; 17: e18780.
 21. Witkin JM, Newman AH, Nowak G, et al. Role of dopamine D1 receptors in the lethal effects of cocaine and a quaternary methiodide analog. *J Pharmacol Exp Ther* 1993; 267: 266–274.
 22. Alldredge BK. Seizure risk associated with psychotropic drugs: clinical and pharmacokinetic considerations. *Neurology* 1999; 53: S68–S75.
 23. Hollander JE and Hoffman RS. Cocaine. In: Goldfrank LS, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS and Nelson LS (eds) *Goldfrank's toxicologic emergencies*. 7th ed. New York: McGraw-Hill, 2003, pp.1004–1019.
 24. Lertxundi U, Hernandez R, Medrano J, et al. Antipsychotics and seizures: higher risk with atypicals? *Seizure* 2013; 22: 141–143.
 25. Liang CS, Yang FW and Chiang KT. Paliperidone-associated seizure after discontinuation of sodium valproate: a case report. *J Clin Psychopharmacol* 2011; 31: 246–247.
 26. Arora M and Arndorfer L. EEG abnormalities in a patient taking aripiprazole. *Psychiatry (Edgmont)* 2007; 4: 18–19.
 27. Shao SC, Wu WH, Yang YK, et al. Quetiapine-induced absence seizures in a dementia patient. *Geriatr Gerontol Int* 2016; 16: 1168–1171.
 28. Prescribing information for aripiprazole. In: *Physician's Desk Reference*. 61st ed. Montvale, NJ: Medical Economics, 2006.
 29. Tsai JF. Aripiprazole-associated seizure. *J Clin Psychiatry* 2006; 67: 995–956.
 30. Centorrino F, Price B, Tuttle M, et al. EEG abnormalities during treatment with typical and atypical antipsychotics. *Am J Psychiatry* 2002; 159: 109–115.
 31. Zhang T, Zheng X, Zhou Z, et al. Clinical potential of an enzyme-based novel therapy for cocaine overdose. *Sci Rep* 2017; 7: 15303.
 32. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human

- dopamine D2 receptors. *J Pharmacol Exp Ther* 2002; 302: 381–389.
33. Jibson MD. Second-generation antipsychotic medications: Pharmacology, administration, and side effects. UpToDate®, https://www.uptodate.com/contents/second-generation-antipsychotic-medications-pharmacology-administration-and-side-effects?search=second-generation-antipsychotic&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1 (2019, accessed 25 May 2019).
34. Nemeroff CB, Kinkead B and Goldstein J. Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing. *J Clin Psychiatry* 2002; 63: 5–11.
35. Heard K, Palmer R and Zahniser NR. Mechanisms of acute cocaine toxicity. *Open Pharmacol* 2008; 2: 70–78.
36. Derlet RW, Albertson TE and Rice P. The effect of SCH 23390 against toxic doses of cocaine, d-amphetamine and methamphetamine. *Life Sci* 1990; 47: 821–827.
37. Derlet RW, Albertson TE and Rice P. The effect of haloperidol in cocaine and amphetamine intoxication. *J Emerg Med* 1989; 7: 633–637.
38. Mittleman MA, Mintzer D, Maclure M, et al. Triggering of myocardial infarction by cocaine. *Circulation* 1999; 99: 2737–2241.