Letters to the Editor

Effects of "Ecstasy" Blocked by Serotonin Reuptake Inhibitors

Sir: 3,4-Methylenedioxymethamphetamine (MDMA), better known as Ecstasy, is a synthetic amphetamine analog that can be classified as a phenethylamine-type hallucinogen. The drug is commonly linked with "rave" dance parties, and its use has become increasingly prevalent in recent years.[1] The primary mechanism of action of this agent is thought to be via indirect serotonergic agonist effects with release of serotonin stores and blocking of serotonin reuptake, although the drug also affects other neurotransmitter systems.[2,3]

MDMA appears to be taken up by neurons through a fluoxetine-sensitive carrier mechanism; preclinical studies indicate that fluoxetine attenuates MDMA-induced serotonin release in prefrontal cortex and striatum in a dose-dependent fashion.[4] However, there are clinical reports that fluoxetine taken together with MDMA ingestion did not interfere with the subjective effects of this agent.[5] We report 2 patients in whom concurrent chronic use of a selective serotonin reuptake inhibitor (SSRI) resulted in blocking the usual subjective effects of MDMA.

Case 1. Ms. A, a 21-year-old patient, presented with trichotillomania for which citalopram, a highly selective SRI, was prescribed at 20 mg/day. Ms. A was an occasional user of Ecstasy, but had not reported use for some months. After several months of citalopram treatment, she attended a rave and had her usual dose of Ecstasy—one half of a tablet. She reported that instead of the typical subjective "rush" that she experienced on this drug, she felt as though she had not in fact taken any substance.

Case 2. Ms. B, a 19-year-old patient, presented with trichotillomania for which she was treated with paroxetine at 20 mg/day for several months. She then started attending raves, and tried Ecstasy. She felt no effects at all from this agent. In contrast, the use of amphetamines did result in a high. Ms. B elected to discontinue paroxetine to see whether this would allow her to experience an Ecstasy high. In the absence of paroxetine, she was in fact able to do so.

These 2 case reports are consistent with the hypothesis that MDMA or a metabolic derivative must be taken up by a serotonin reuptake mechanism to exert its effects. Alternatively, given previous reports that SSRIs, which down-regulate 5-HT$_2$ receptors after chronic administration, block the psychedelic effects of other hallucinogenic 5-HT$_2$ agonists such as lysergic acid diethylamide (LSD),[6] a postsynaptic mechanism for the effects noted here could be hypothesized.

Differences in MDMA effects between these cases and previously published reports[5] may reflect the fact that in the earlier cases fluoxetine was not used on a chronic basis prior to MDMA use. We cannot, of course, exclude the possibility that our patients received an agent other than MDMA. It may be speculated that SSRIs could be useful in helping patients who have difficulty stopping Ecstasy use, although the possibility of adverse interactions between SSRIs and Ecstasy should also be borne in mind.[7]

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Dan J. Stein, M.B.
Jeffrey Rink, M.A.
Cape Town, South Africa

Chorea and Tardive Dyskinesia in a Patient Taking Risperidone

Sir: The antipsychotic risperidone has been available in the United States since 1994.[1] It has been widely used, as studies have shown that extrapyramidal symptoms are less common than with other antipsychotics,[2] and that the incidence of side effects causing discontinuation is low.[1] Risperidone was also shown to be effective and have minimal side effects in adolescents[3] and children.[4] Over time, other, more significant potential side effects have been identified: neuroleptic malignant syndrome,[5–8] lengthening of the QT interval,[9] obsessive-compulsive disorder,[10,11] and tardive dyskinesia.[12–15] There have been no reports of chorea in association with risperidone in the literature. We report a case of chorea and tardive dyskinesia associated with risperidone use.

Case report. Ms. A, a 13^1/$_2$-year-old white female, had a family history of depression, enmeshment, and benign neglect and a personal history of aggression, defiance, and noncompliance at the time she transferred her care to one of the authors (N.B.C.). Although she had taken many different psychiatric medications in the past, her medical history was available only from her family; previous medical records were unavailable. According to family report, risperidone had been the most effective medication in controlling her symptoms, especially aggression. At the time of transfer, Ms. A was taking risperidone, 6 mg/day. She had been taking risperidone for almost a year. She was doing well in a class for severely behaviorally handicapped

Table 1. Time Line of Events[a]

Time	Events
First visit	Transfers care to N.B.C.; on risperidone, 6 mg/d; AIMS: mild hand-dangling movement and tongue protrusion
Months after first visit	
3 months	AIMS: minimal open mouth movement and tongue protrusion
4 months	Mild hand tremors (later resolved)
6 months	Fluoxetine initiated for depressive symptoms
7 months	By family report: doing well in school, behavior improved; trazodone initiated for trouble sleeping
8 months	Sleeping better; AIMS: pronounced involuntary oral-buccal twitches, right to left spillover of hands with rapid alternating movements, leg stiffness; risperidone decreased to 2 mg bid
9 months	Behavioral tics; neurology referral; risperidone decreased to 1 mg bid; later that month, school indicates severe deterioration had occurred over previous school year; risperidone decreased to 1 mg qhs and then discontinued
10 months	Chorealike movements evident during office visit; soonest neurology appointment not for 2 months; aggression and defiance worsening; medical evaluation obtained; all medication stopped
12 months	Aggression and defiance improved; movements decreased
16 months	Movement disorder resolved

[a]Abbreviation: AIMS = Abnormal Involuntary Movement Scale.

individuals. On the basis of Abnormal Involuntary Movement Scale (AIMS) assessment, she had mild hand-dangling movement and tongue-protrusion.

Three months after her first visit, Ms. A had minimal open mouth movement and tongue protrusion as indicated by the AIMS (Table 1). Four months after the first visit, she reported mild hand tremors, which subsequently improved. At month 6, she was started on fluoxetine, 10 mg every other day, for depressive symptoms. At month 7, her family reported that she was doing well in school and her behavior had improved, but that she was having trouble sleeping. She was started on trazodone, 25 mg at bedtime. At month 8, Ms. A was sleeping better; however, she had, as indicated by the AIMS, pronounced involuntary oral-buccal twitches, right-to-left spillover of her hands with rapid alternating movements, as well as stiffness of her legs. Risperidone was decreased to 2 mg twice a day.

Nine months after her first visit, Ms. A complained of "jerky movements" at times and "difficulty moving her legs." These were believed to be behavioral tics. It was recommended that she see her neurologist, and risperidone was decreased to 1 mg twice a day. Later that month, the school informed the psychiatrist that Ms. A's condition had deteriorated over the previous school year and that excessive eye blinking, stuttering, shaking of hands and legs, decreased ability to communicate orally, declining handwriting ability, jerky arm and leg movements, and decreased eye-hand coordination had been observed. Her risperidone was decreased to 1 mg at bedtime and then discontinued. At month 10, the above movements were visible during the office visit. A neurology follow-up appointment was unable to be scheduled for 2 months. Later that month, Ms. A was exhibiting chorea-type movements, and her aggression and defiance

had worsened because she was taking no antipsychotic medication. Prompt medical evaluation was obtained.

At the time of medical referral (to K.E.B. and R.T.S.), in addition to the behaviors reported by the school, Ms. A, according to family report, had been holding her hand in a "serving platter" fashion and had bilateral in-toeing when she walked. When Ms. A was stressed or nervous, her symptoms were worse. Symptoms abated when she was sleeping. There was no change in symptoms with hot showers or baths, and she made no complaints of weakness, numb sensations, tingling, or loss of balance. She had no weight loss, night sweats, or heart palpitations. She was not taking hormonal contraception. Approximately 1 month after she transferred her care to N.B.C., Ms. A reported a sore throat and mild bilateral knee arthralgia, but no chest pain, rashes, or significant fever. According to the family, she was not seen by a physician at that time because of the relative insignificance of her symptoms.

At the time of her medical referral, Ms. A's medications included trazodone, 25 mg p.o. q.h.s.; fluoxetine, 10 mg p.o. every other day; and terfenadine, 60 mg p.o. q.d. p.r.n. Her mother reported that Ms. A's past medical history was significant for oppositional defiant disorder, hyperactivity disorder, mild depression, and seasonal allergies. She was a product of a normal full-term pregnancy and delivery, and she had achieved developmental milestones at appropriate times. In a workup for violent behavior when Ms. A was about 2 years of age, the family reported that neurologists determined that she had had a "perinatal right-sided brain injury." There was no family history of dyskinesia, tics, or Huntington's chorea. Her family, and social history and review of systems, except as mentioned above, were not otherwise contributory.

Ms. A was alert, oriented, and very cooperative at the time of the physical examination. The content of her speech was appropriate; however, it was frequently interrupted by tongue protrusions or facial movements. Her gait was minimally widened with bilateral in-toeing; balance was otherwise intact. She had difficulty with rapid alternating movements and eye-hand coordination. During the interview and examination, Ms. A repeatedly revolved her hand throughout the range of wrist flexion and extension. She was noted to cock her head to either side frequently, and she had repeated nonballistic, asymmetrical, jerky movements of her upper extremities. When she sat, her feet were in plantar flexion with only the balls of her feet in contact with the floor. Choreiform movements of her upper extremities increased when she walked.

Due to initial concern regarding Sydenham's chorea, Ms. A was treated with 1.2 million units of a penicillin G benzathine and penicillin G procaine suspension when the evaluation was initiated. Her evaluation included normal results for throat culture; electrolytes; liver and kidney function tests; thyroid function tests; ASO, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, and anti–native DNA antibody measurements; Epstein-Barr virus, cytomegalovirus, mycoplasma, and Lyme disease titers; lead level; and electrocardiogram. An echocardiogram showed a structurally normal heart, mild pulmonary insufficiency, and trivial-to-mild mitral regurgitation. Penicillin treatment was discontinued owing to a paucity of confirmatory findings.

Ms. A received a neurology consultation as well as a second opinion. An electroencephalogram (EEG) showed intermittent slowing of the background rhythms without epileptiform abnormalities, which could be consistent with encephalopathy due to medication or other causes. Results of a second EEG 1 month later were similar but improved, so evaluation for other causes of encephalopathy was not indicated. Both magnetic resonance imaging and brain single pho-

ton emission computerized tomography (SPECT) imaging were unremarkable.

Consultation with both neurologists and presentation to the Department of Pediatrics did not lead to a definitive diagnosis, but led to agreement that Ms. A exhibited both tardive dyskinesia and choreiform movements, even after the medication had been discontinued for some time.

Twelve months after her first visit (to N.B.C.), Ms. A's aggression and defiance were improved, and the movements were decreased. By 16 months after her first visit, there was no longer evidence of the prior movement disorder by observation or the AIMS.

Tardive dyskinesia has been associated with neuroleptic medications, including risperidone,[12–15] although it initially appeared that risperidone would have a lower incidence of side effects than other neuroleptic medications.[2] Chorea has also been associated with neuroleptics[16]; however, there are no reports in the literature regarding chorea in association with risperidone.

This patient was evaluated for many conditions associated with tardive dyskinesia[17] and chorea.[16,18] The authors believe that her tardive dyskinesia and choreiform movements may have been a side effect of risperidone, as her workup did not provide an alternative diagnosis. It is possible that her condition was related to fluoxetine treatment or risperidone withdrawal; however, the behaviors reported by her school most likely indicate an onset prior to initiation of fluoxetine and risperidone withdrawal. A more clear connection between potential causes and effects is limited due to reliance on family report and delay in gaining information from the school. It appears from the school report that this patient was experiencing impairment in functioning when the parents were reporting that she was doing well. Unfortunately, the school's information was not available until several months after Ms. A's care was transferred to the first author.

Despite widespread acceptance of risperidone use in children and adolescents, the drug may have side effects that were previously unrecognized. This case emphasizes the potential for medication-induced movement disorders that cause impairment of daily functioning and have long-term effects. The authors urge caution in the selection of medications prescribed for behavioral control, as well as careful and frequent monitoring with a standardized scale such as the AIMS, as the risk-benefit ratio of the medications may be unknown. Using the lowest possible effective dosage would also be prudent. Further evaluation of risperidone and delineation of its side effects are warranted.

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Nancy B. Carroll, M.D.
Kathryn E. Boehm, M.D.
R. Todd Strickland, M.D.
Toledo, Ohio

Clozapine Versus Risperidone in Treatment-Refractory Schizophrenia: Possible Impact of Dosing Strategies

Sir: We read with interest the recent article by Lindenmayer et al.[1] concerning the comparison of clozapine versus risperidone in 35 treatment-refractory schizophrenic patients. In the 12-week open-label study, both medications were effective across a wide spectrum of psychopathologic measures, with clozapine being numerically superior to risperidone. In addition, clozapine was associated with fewer extrapyramidal side effects. Noteworthily, their risperidone dosing strategy, albeit consistent then with manufacturer-provided labeling, merits further deliberation today. Clozapine treatment was aimed at reaching a minimum dose of 400 mg/day or a minimum plasma clozapine level of 350 ng/mL at week 4. The dose of risperidone was titrated to 6 mg/day in 3 days, with gradual escalation up to 16 mg/day if response was insufficient. As a result, mean ± SD clozapine daily dose was 363.02 ± 90.73 mg, and mean risperidone daily dose was 8.95 ± 1.76 mg. Initially, the North American multicenter trials[2,3] revealed a bell-shaped dose-response curve for risperidone with the optimal efficacy occurring at a daily dosage of 6 mg. Recently, clinical practice with risperidone has involved efforts to use doses of 4 to 6 mg/day[4,5] or lower.[6]

Lindenmayer et al.[1] indicated that their high risperidone doses may have contributed to the greater risk of extrapyramidal side effects observed in the risperidone group. Nevertheless, they did not discuss the possible detrimental effect of excessively high doses on risperidone's efficacy.[2–4,6–8] It has been suggested that the appearance of risperidone-related extrapyramidal side effects may be an indicator of unduly high doses and, consequently, poor clinical efficacy.[6,8] Therefore, the higher incidence of extrapyramidal symptoms in their risperidone group may have reflected utilization of unnecessarily high doses.

Furthermore, their clozapine-treated patients showed a progressive improvement over the entire treatment period. In contrast, their risperidone recipients improved significantly in the beginning stages (by the end of the second week) of the trial and

remained stable thereafter.[1] We wonder if their titration tactics may have played a role in this discrepancy. The authors did not reveal the doses used at assessment visits other than the endpoint. However, it may be imperative to examine whether a portion of risperidone patients received unusually high doses, especially during the later treatment stages. The doses of risperidone higher than recommended today may have circumscribed further clinical improvements.[6] Likewise, in a 28-week double-blind study[5] comparing olanzapine and risperidone in the treatment of schizophrenia and other psychotic disorders, the most frequently administered dose of risperidone was 7.2 ± 2.7 mg/day (mean ± SD), which has been recently considered perhaps too high to obtain maximum results.[6]

Can risperidone at somewhat lower doses actually bring a better effect in treatment-refractory schizophrenic patients than that revealed in the Lindenmayer et al.[1] study? An earlier 8-week double-blind trial by Bondolfi et al.[9] has also compared the efficacy of clozapine (mean dose = 291.2 mg/day) and risperidone (mean dose = 6.4 mg/day) in 86 schizophrenic patients who had been resistant to or intolerant of conventional neuroleptics. Plasma levels of clozapine were measured in 28 of 43 clozapine receivers; the mean levels were 292 ng/mL in the clozapine nonresponders and 281 ng/mL in the responders. Both agents were found to be equally effective at treatment endpoints. More risperidone patients than clozapine patients responded to treatment by week 1 and week 2, and more clozapine patients may have responded during week 3. Finally, both medications were associated with similarly gradual improvements from week 4 to week 8.[9] The incidence of extrapyramidal symptoms was comparably low in the 2 groups.[9] Of note, the mean clozapine dose of 291.2 mg/day approximates the average clozapine dose (283.7 mg/day) used in Europe,[10] but is lower than the mean dose (444 mg/day) used in the United States.[10] Moreover, the mean plasma clozapine concentration achieved in the Bondolfi et al. trial[9] is below the recommended threshold level of 350 to 420 ng/mL for clinical response,[11–15] perhaps biasing the comparison in favor of risperidone. On the other hand, VanderZwaag et al.[16] have recently shown that, if an equally divided dosing regimen is being used and blood is drawn about 12 hours after the last dose, lower plasma clozapine levels (250 to 300 ng/mL) can be effective as well and may cause fewer side effects.

Further studies are required to validate the clozapine dose (or plasma concentration) relationships with clinical response. In addition, the generalizability of the Bondolfi et al. results[9] may be further impeded by the limited sample size, heterogeneous patient populations (both treatment-resistant and treatment-intolerant patients), and a rather short-term (8-week) treatment period. Recent reports have indicated that some patients may not show response until 3 to 12 months from clozapine initiation.[17] With regard to risperidone in the treatment of refractory schizophrenia, Marder[18] has considered a minimum trial to be about 3 months. To our knowledge, however, the delayed onset of risperidone effects in refractory schizophrenic patients has not been documented even in case reports. Currently, we have experience with a treatment-refractory schizophrenic inpatient whose response to 4 mg/day of risperidone occurred only after 14 weeks of therapy (H.-Y. L., unpublished data). Certainly, we urge caution in making any conclusions based on the observation of a single patient.

When 2 drugs are compared in a clinical trial, response rates of each drug may vary with doses.[6] To date, the optimum dosing strategy of risperidone (or even clozapine[10–16]) for treatment-resistant schizophrenia remains to be determined. Therefore, for appropriately comparing clozapine and risperidone in the man-

agement of medication-resistant schizophrenia, long-term, larger scale, controlled studies of various daily regimens (for instance, 300 mg, 400 mg, and 500 mg of clozapine versus 4 mg, 6 mg, and 9 mg of risperidone) are warranted.

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Hsien-Yuan Lane, M.D.
Wen-Ho Chang, M.D.
Taipei, Taiwan