

Is Statin Use Safe in Individuals With Psychotic Disorders?

Sir: Individuals with schizophrenia and other serious mental illnesses have a mortality rate at least 2 times as high as those without psychotic disorders, with the excess mortality largely attributed to higher rates of death from cardiovascular disease.¹

Wider use of cholesterol-lowering drugs (statins) to reduce cardiovascular risk in this setting has been suggested.^{2,3} However, widespread use of statin drugs in individuals with psychotic disorders may raise some concerns.

Accumulating evidence suggests a relation between low cholesterol and violence, aggression, and hostility,⁴⁻⁶ notwithstanding that the biological basis for attributing causality for behavioral disorders and hypocholesterolemia is not clear.⁵ Indeed, decreased cholesterol levels seem to indicate a population at risk for parasuicide or completed suicide,⁷ and follow-up studies have found that individuals with lower cholesterol levels have an increased risk of completing suicide.⁸ Moreover, the inheritance of defects leading to low cholesterol levels could predispose individuals to violent and suicidal behavior.^{9,10} Interestingly, among patients with schizoaffective disorders, suicidal individuals have been shown to have statistically significantly lower levels of cholesterol than nonsuicidal patients.¹¹ Of note, to the best of our knowledge, there has been no randomized trial evaluating the safety and efficacy of statins in patients with psychotic disorders.

On the other hand, randomized trials with statins have not shown a definite association between cholesterol-lowering treatment and non-illness-related mortality from suicides, accidents, and violence. However, statin trials are specifically designed to test drug efficacy, often with run-in phases. Investigators usually conduct the studies in groups of patients who have few comorbidities and are not using many concomitant medications. Furthermore, when side effects are measured, their seriousness and severity are not graded. Indeed, in real-world clinical practice, it has been suggested that severe anger and irritability may occur in some statin users.¹²

Finally, lifestyle advice, especially recommendation of physical activity, should be regarded as the cornerstone of cardiovascular disease prevention in patients with schizophrenia.¹³ However, statin-related muscular complaints (the most frequent statin-related side effects) might interfere with the implementation of exercise.¹⁴ These side effects are of particular concern in a population with psychotic disorders who frequently experience motivation and energy problems, symptoms that fundamentally reduce their capacity for regular physical activity.

The almost total focus on lowering cholesterol through the use of drugs can distract attention from relatively simple lifestyle changes that can achieve greater reductions in risk of cardiovascular disease in patients with serious mental illnesses.

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High-Risk Groups for Charcoal-Burning Suicide in Taiwan, 2001-2005

Sir: Suicide by charcoal burning, in which the victim dies from carbon monoxide poisoning, has been an epidemic in Hong Kong and Taiwan for some years now.^{1,2} Following wide publicity attending the first case in late 1998 in Hong Kong, disseminated through the media and Internet, the suicide rate from charcoal burning and other poisonous gases in Taiwan has increased dramatically, from 0.14 per 100,000 in 1998 to 5.38 per 100,000 in 2005, a 40-fold increase. In 1998, only 32 people were reported to have used charcoal burning or other poisonous gases to kill themselves in Taiwan, and these deaths accounted for only 1% (32/2906) of all suicides and deaths from undetermined intent. By 2005, this proportion had increased to 27% (1346/4987). Charcoal burning is now the second most commonly employed method of suicide in Taiwan, and it has been since 2002,^{3,4} but little is known about the epidemiologic profile of the people who use this suicide method. This aim of this study was to identify sociodemographic groups that are at increased risk of suicide by charcoal burning in Taiwan.

Table 1. Sociodemographic Data for Groups at High Risk of Suicide, According to Method, in Taiwan, 2001–2005

Group	Charcoal Burning				Pesticide Poisoning				Hanging			
	Deaths, N	Rate ^a	MRR ^b	95% CI	Deaths, N	Rate ^a	MRR ^b	95% CI	Deaths, N	Rate ^a	MRR ^b	95% CI
Urban men, aged ≥ 65 y	50	1.9	3.8	2.5 to 5.7	87	3.3	12.4	7.9 to 19.4	716	27.2	45.2 ^c	34.3 to 59.6
Rural men, aged ≥ 65 y	15	0.6	1.1	0.6 to 2.1	425	16.3	60.9 ^c	40.4 to 91.9	642	24.6	40.9	31.0 to 54.0
Urban men, aged 45–64 y	489	7.6	15.1	11.1 to 20.5	215	3.3	12.5	8.2 to 19.0	857	13.3	22.1	16.8 to 29.0
Rural men, aged 45–64 y	280	5.2	10.3	7.5 to 14.1	613	11.3	42.2	28.1 to 63.5	739	13.6	22.6	17.2 to 29.8
Urban men, aged 25–44 y	1050	10.4	20.8 ^c	15.5 to 28.1	154	1.5	5.7	3.7 to 8.8	730	7.3	12.1	9.2 to 15.9
Rural men, aged 25–44 y	764	8.5	17.0	12.6 to 23.0	534	6.0	22.3	14.8 to 33.6	801	8.9	14.9	11.3 to 19.6
Urban men, aged ≤ 24 y	129	1.1	2.3	1.6 to 3.2	13	0.1	0.4	0.2 to 0.8	143	1.3	2.1	1.5 to 2.8
Rural men, aged ≤ 24 y	112	1.2	2.3	1.6 to 3.3	73	0.8	2.8	1.8 to 4.5	142	1.5	2.4	1.8 to 3.3
Urban women, aged ≥ 65 y	9	0.4	0.7	0.4 to 1.5	64	2.7	10.0	6.3 to 16.0	284	11.8	19.7	14.7 to 26.4
Rural women, aged ≥ 65 y	6	0.2	0.5	0.2 to 1.1	246	9.4	35.3	23.2 to 53.7	322	12.4	20.6	15.4 to 27.4
Urban women, aged 45–64 y	173	2.5	5.0	3.6 to 6.9	85	1.2	4.6	2.9 to 7.2	342	4.9	8.2	6.2 to 11.0
Rural women, aged 45–64 y	64	1.3	2.5	1.7 to 3.7	246	4.8	18.2	11.9 to 27.6	249	4.9	8.2	6.1 to 11.0
Urban women, aged 25–44 y	448	4.2	8.4	6.2 to 11.4	42	0.4	1.5	0.9 to 2.4	275	2.6	4.3	3.2 to 5.8
Rural women, aged 25–44 y	259	3.3	6.6	4.8 to 9.0	165	2.1	7.9	5.1 to 12.0	229	2.9	4.8	3.6 to 6.5
Urban women, aged ≤ 24 y	68	0.6	1.3	0.9 to 1.9	10	0.1	0.4	0.2 to 0.7	71	0.7	1.1	0.8 to 1.6
Rural women, aged ≤ 24 y	45	0.5	1.0	Reference	24	0.3	1.0	Reference	54	0.6	1.0	Reference

^aMortality rate (deaths/100,000).

^bMRR according to Poisson regression model.

^cThe highest mortality ratio among the 3 suicide methods.

Abbreviation: MRR = mortality rate ratio.

Method. Mortality data for all deaths classified as suicide or death of undetermined intent between January 2001 and December 2005 were collected electronically from the Department of Health of the Executive Yuan of Taiwan (Taipei, Taiwan). A previous Taiwanese study indicated that many presumed suicides are actually reported as death of undetermined intent; therefore, data relating to these deaths were also included in the study.⁵ Age- and sex-specific suicide rates were calculated for both urban and rural areas. Mortality rate ratios (MRRs) and 95% CIs for each sociodemographic group were calculated for different suicide methods according to the Poisson regression model. Different methods of suicide carry different ICD-10 codes; X67 and Y17 are related to charcoal burning, whereas X68 and Y18 are for pesticide poisoning, and X70 and Y20 are for hanging.

Results. Between January 2001 and December 2005 in Taiwan, 3961 people used charcoal burning, 2996 used pesticide poisoning, and 6596 used hanging to die by suicide. Table 1 shows how age, sex, and geographic location have interdependent effects on the likelihood of use of different suicide methods (Table 1). It is apparent that males aged between 25 and 44 years who live in urban areas are at the highest risk from suicide by charcoal burning. This sociodemographic group constituted one quarter (1036/3899) of all deaths by charcoal burning. Furthermore, it can be seen that men aged 65 or above are more likely to use pesticide poisoning to die by suicide if they live in rural areas and hanging if they live in urban areas.

Our findings indicate that men aged 25 to 44 years who live in urban areas are the most likely to use charcoal burning to die by suicide, but this phenomenon is by no means exclusively confined to these areas. Of the 3961 suicides by charcoal burning between 2001 and 2005 in Taiwan, two fifths (1549/3961) were in rural areas. Suicide rates by charcoal burning did not differ significantly between urban and rural areas. The MRR was 1.32 (95% CI = 1.23 to 1.41) after adjusting for age and sex.

Age appears to be the most important factor when predicting different suicide methods. Suicide rates from pesticide poisoning and hanging increase with age, while the peak incidence of suicide by charcoal burning was with people aged 25 to 44

years. A similar pattern has been observed in Hong Kong: subjects were predominantly middle-aged and economically active, with no preexisting history of substance abuse or other mental disorders.⁶

One of the strengths of this study is the large sample size (number of deaths), which has enabled detailed stratification of different sociodemographic groups. Sampling across a diverse range of regions in Taiwan has allowed the effect of urbanization to be explored fully. Use of the Poisson regression model has also made estimation of risks for the different sociodemographic groups to be more robust.

One of the limitations of this study is that some deaths classified as being caused by other gases (not charcoal burning) may have created a bias that could skew the distribution of any particular sociodemographic group. Another limitation is that only information recorded on the death certificate could be used. Plenty of information relating to the deceased (e.g., income, employment status, previous psychiatric history, and motivation for suicide) and actual circumstances (e.g., where the charcoal was purchased and burned) was not available in this study. Despite this limitation, suggestions of the circumstances leading to suicide by charcoal burning in some of the men aged between 25 and 44 years could be obtained from the local newspaper reports at the time of the event. Similar to the findings by Chan and colleagues in Hong Kong,⁶ overindebtedness was the most commonly mentioned reason relating to these deaths.

With regard to the implications for suicide prevention, it is not entirely clear how deaths in this high-risk group can be prevented beyond a standard 2-pronged intervention strategy of restricting access to charcoal and increasing general awareness in the media. Yip and Lee also recommend that astute gatekeepers raise an alarm. Security guards are common outside residential buildings in both Hong Kong and Taiwan, and they could recognize that bags of charcoal, duct tape, alcohol, and drugs are obviously not for a barbecue when there are no meats or snacks also present.² Our sociodemographic findings may aid security guards (or relatives, classmates, colleagues, or neighbors) in recognizing at-risk subjects and help to make an intervention that could prevent these unnecessary deaths.

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Toxic Psychosis After Intake of the Hallucinogen Salvinorin A

Sir: The hallucinogenic sage *Salvia divinorum* (*S. divinorum*) is known by many names, including *ska Maria*, *ska Pastora*, *hojas de Maria*, and many others. Despite its many names, *S. divinorum* was not identified until 1962, when Wasson and Hofmann collected a member of the Lamiaceae (mint) family that was known by the Mazatec people of Oaxaca, Mexico, to have psychoactive properties.¹ In recent years, *S. divinorum* has become widely available throughout the world, via numerous internet suppliers, either as leaves or as concentrated extracts. Young adults and adolescents have begun to smoke the leaves and leaf extracts of the plant to induce powerful hallucinations.

Salvinorin A, which is the main active drug in *S. divinorum*, is a structurally unique furanolactone neoclerodane diterpene. Salvinorin A is both pharmacologically and chemically unique in that it represents the first non-nitrogenous, naturally occurring κ -opioid receptor (KOR) selective agonist and the only known non-alkaloidal hallucinogen.²

Behavioral effects of salvinorin A are known to be significantly blocked by pretreatment with nor-binaltorphimine, a κ -opioid antagonist and the cannabinoid type 1 (CB₁) antagonist rimonabant, suggesting that the central nervous effects are specifically mediated by both κ -opioid and cannabinoid CB₁ receptors.

The leaves and extracts of *S. divinorum* have been used to create both hallucinatory and mind-expanding effects.³ Attraction to the drug among recreational users can be attributed to

hallucinogenic effects, which in doses above 200 μg rival the synthetic hallucinogen lysergic acid diethylamide (LSD) in doses of 50–250 μg .³ *S. divinorum* product abusers experience a psychic depersonalization condition, a unique sensation of being disconnected from one's body.

When leaves of *S. divinorum* are chewed or smoked, exposed individuals describe an intensely positive hallucinogenic experience (e.g., altered depth perception, heightened sensual and aesthetic appreciation, a creative dream-like state). However, depending on the dose and the route of administration, the effects are sometimes extremely negative (overly-intense experiences; fear, terror, and panic; increased perspiration; and possible difficulty integrating experiences).

Until now, the potential abuse of salvinorin A and especially concomitant psychiatric symptoms or diseases have been poorly investigated.

We therefore report a case of an 18-year-old female patient who unwittingly ingested *S. divinorum* for the first time, leading to a severe toxic psychosis within a week after intake with devastating somatic consequences resulting in a long-lasting interdisciplinary medical treatment and physical impairment.

Case report. Ms. A was an 18-year-old female patient admitted to our psychiatric emergency service with acute onset of agitation, disorganization, and hallucinating behavior after smoking cannabis. A few days after admission, her former boyfriend disclosed that she had also unknowingly smoked the leaves and leaf extracts of *S. divinorum*, which had been added to her marijuana cigarette, for the first time. The patient had a long history of use of cannabis but had never experienced a psychotic episode.

Ms. A was admitted to a general psychiatric ward with the presumptive diagnosis of a substance-induced psychotic disorder (ICD-10 criteria) and subsequent schizophrenia-spectrum disorder. After showing more and more self-mutilating behavior, with massive disorganization, disorientation and the intention to quit treatment, she was legally committed to a closed ward for involuntary treatment. There was no response to antipsychotic treatment with intramuscular olanzapine (up to 30 mg/day) or intravenous haloperidol (up to 15 mg/day), and Ms. A remained highly psychotic, with disordered thinking, thought blocking, derealization or delusional perceptions, and slow speech.

During one of the following nights, Ms. A showed a marked decrease of alertness that required an immediate transfer to an intensive care unit. Because of a developing toxic psychosis with stupor and catatonic excitement, potential neuroleptic-associated elevation of creatine kinase to 2055 U/L, and the lack of efficacy of the ongoing antipsychotic medication, further treatment was required. Ms. A then underwent 2 rounds of emergency electroconvulsive therapy (ECT), but these were discontinued after she developed recurrent self-limited asystolias with a maximum duration of 5 seconds. Although there was no further ECT treatment, Ms. A experienced recurrent cardiac arrhythmias that required a temporary external cardiac pacemaker.

A recurring acute agitation led to a traumatic amputation of a 1 cm \times 1 cm part of Ms. A's tongue with a subsequent aspiration leading to a temporary intubation and ventilation. Shortly after that, Ms. A developed elevated temperature and a drop in blood pressure that required catecholamine treatment. Within hours, the abdomen became tense and inflated, and the ultrasound and x-ray showed signs of peritonitis and an atony of the bowels. A following explorative laparotomy showed multiple segmental necroses of the distal small intestine and the ascending colon, so that these parts had to be removed surgically. Thereafter we

started a serum-blood-level controlled antipsychotic treatment with clozapine up to 300 mg (reaching serum drug levels of 355 µg/L clozapine and 148 µg/L norclozapine). Slowly but surely, Ms. A's psychopathology improved, her psychotic symptoms disappeared, and she was relocated to the psychiatric department. As she requested termination of the clozapine treatment, we shifted to a low-dose treatment with olanzapine, 7.5 mg/day. Ms. A was then discharged in stable psychiatric condition. After the long course of the disease and the devastating somatic consequences, Ms. A and her parents decided to institute legal proceedings against the former friend of the patient who was accused of having administered *S. divinorum* unbeknownst to the patient.

A forensic-toxicological investigation of the patient's hair revealed the use of cannabinoids in the past but could not reveal the use of salvinorin A. A principal verifiability of salvinorin A has not yet been investigated systematically and may be difficult to establish due to the short half-life of the diterpene, which seems to be eliminated in blood quite rapidly, finding a mean \pm SD elimination half-life of 56.6 ± 25 minutes in nonhuman primates.⁴

Human salvinorin A effects, consistent with κ -opioid receptor agonism, include antinociception, sedation, dysphoria, and distorted perceptions. The illicit use of easily available hallucinogenic compounds, like salvinorin A, is a reemerging health problem, particularly among well-educated young adults and teens.^{5,6}

In the present case, salvinorin A was unwittingly used by smoking the leaves of *S. divinorum*. Beyond the described short-lived inebriant states with intense, bizarre feelings of depersonalization,⁷ our patient developed a very long-lasting psychotic status. In this special case, several somatic consequences are reported, which are likely attributable to the medical treatment of a severe psychotic state rather than to the psychosis itself. Nevertheless, our observations of the dramatic course of the patient's disease contradict supporters of recreational *S. divinorum* use who claim that, while certain elements in the drug experience may cause discomfort, bad experiences are likely to be outweighed by positive experiences.^{8,9}

The presented single case report shows significant effects of *S. divinorum* on the onset of severe psychotic symptoms leading to a symptomatic toxic psychosis with emerging and life-threatening medical consequences. Based on the selectivity of salvinorin A for the KOR and its potential to induce a short-lived inebriant psychotic state with intense, bizarre feelings of depersonalization, the KOR represents a potential molecular

target for the development of drugs to treat disorders characterized by alterations in perception, including schizophrenia.

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