Acute toxic effects related to 4-fluoroamphetamine

The Monitor Drug-related Incidents (MDI) is a Dutch monitoring system initiated in 2009, which collects data on drug users who present to medical services with acute toxic effects related to recreational drug use. We have observed a rapid and substantial increase in the number of acute toxic effects related to the use of the new psychoactive substance (NPS) 4-fluoroamphetamine (4-FA or 4-FMP) in the Netherlands, together with several reports of life-threatening complications.

The stimulant 4-FA started as an adulterant in common recreational drugs, such as amphetamine and ecstasy (MDMA), on the Dutch drugs market between 2007 and 2009, but became a drug of choice in recent years.[1,2] The relatively mild subjective effects were described as an intermediate between amphetamine and MDMA,[1] which might have increased the popularity of this drug.[1,3]

First aid stations at large-scale events reported a considerable increase in 4-FA-related acute toxic effects among young people (median age: 23 years). In 2015, 16% of the acute toxic effects reported by first aid stations of large-scale events were related to the use of 4-FA between January and September, 2016, whereas no toxic effects related to use of 4-FA were reported between 2009 and 2011, less than 1% in 2012 and 2013, 2% in 2014, and 11% in 2015. The Dutch Poisons Information Centre (DPIC), which informs health-care professionals on the management of intoxications, also observed an increase in inquiries about 4-FA intoxications. The DPIC received eight reports about 4-FA intoxications in 2013, 24 in 2014, 44 in 2015, and 33 between January and September, 2016.[4]

Reported clinical effects were similar to those of other amphetamine-like substances (eg, amphetamine and MDMA), such as agitation, tachycardia, hypertension, and hyperthermia. Remarkably, patients with 4-FA intoxications often complain of severe headache. Recently, the MDI and the DPIC received several notifications of severe cardiovascular and cerebrovascular complications, including intracerebral haemorrhages, after the use of 4-FA. The presence of 4-FA was toxicologically confirmed in at least four of these patients. In 2016, at least two people suspected of using 4-FA died in the Netherlands. Although causality is difficult to confirm, health-care professionals should be informed about the life-threatening complications that can occur when treating patients with 4-FA intoxication.

Therefore, we warn for the risk of severe toxic effects following 4-FA use. More research and preventive measures are needed to create awareness about the potential risks among users and to inform health-care professionals about the expected symptoms and possible treatment options of 4-FA intoxications.

We declare no competing interests.

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Biopsy transcriptome expression profiling: proper validation is key

Philip J O'Connell and colleagues (Sept 3, p 983)[1] describe a set of 13 genes they claim has high accuracy for prediction of several chronic allograft damage-related phenotypes in kidney transplants. Because of the large number of genes represented on a microarray chip, rigorous methods must be employed to avoid overfitting. We are concerned that the validation methods in this paper were performed incorrectly, leading to inflated estimates of predictive accuracies.

The authors chose 13 genes after extensive selection and filtering in the development set, and fit the models using penalised logistic regression. The authors used two internal cross-validation methods: repeated threefold cross-validation and leave-one-out cross-validation. In applying cross-validation, all steps—including gene selection—must be reapplied within each training set, without using information from the test sets. The authors did this in the leave-one-out cross-validation (area under the curve [AUC] 0·774). However, the threefold cross-validation seems to use the preselected 13-gene set for all models, producing an AUC of 0·889. This resubstitution method is known to generate inflated accuracy estimates.[2,3] The AUC reported in the Summary and Discussion should not be the unvalidated and clearly overfit 0·967 actually shown, but 0·774. This value is lower than the 0·81 AUC achieved using histoclinical variables