



# FDA - Adverse Event Reporting System (FAERS)

## FOIA Case Report Information

**Case ID: 8464514**

**Case Information:**

**Case Type:** EXPEDITED (15-DAY)    **eSub:** Y    **HP:**    **Country:** AUS    **Outcomes:** OT,    **(A)NDA/BLA:** 014685 /

**FDA Rcvd Date:** 25-Aug-2014    **Mfr Rcvd Date:** 16-Mar-2012    **Mfr Control #:** AU-RANBAXY-2012R1-53740

**Patient Information:**

**Age:** 35 YR    **Sex:** Female    **Weight:**

**Suspect Products:**

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Nortriptyline Hydrochloride	12.5 MG/QD	Unknown	12.5 mg, Daily	Mental disorder		
2	Valerian		Unknown	UNK	Product used for unknown indication		

  

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler
1	Nortriptyline Hydrochloride			U				RANBAXY
2	Valerian			A				

**Event Information:**

**Preferred Term ( MedDRA Version:**    **17.0**    **)**    **ReC**

Akathisia  
 Delirium  
 Drug interaction  
 Homicide  
 Suicidal ideation



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#### Event/Problem Narrative:

This case, manufacturer control number 2012R1-53740 from AUSTRALIA refers to a 35 year old female with the following events (Preferred Terms): Akathisia and Homicide, Suicidal ideation and Delirium .

This case was deemed serious as the reported events were considered to be medically significant.

This case was reported in literature. The literature report consists of 10 case reports and this case refers to Patient 6 of 10.

The patient received following medications which were considered as suspects:

#1) Nortriptyline (Company suspect product) 12.5mg/day for psychological distress

Therapy start date/stop date: Unknown

Action taken: Withdrawn

#2) Valerian for unknown indication

Dose and frequency: Unknown

Therapy start date/stop date: Unknown

Action taken: Withdrawn

As per the report, eleven patients were identified in a study after developing severe akathisia during treatment with antidepressants for psychological distress and various other drugs [some drug details not stated]; they subsequently became suicidal and/or committed or attempted homicide. All were found to have variant CYP450 alleles. All patients recovered from akathisia on withdrawal of the suspect drugs.

A 35-year-old woman started receiving nortriptyline 12.5 mg/day; she had also been taking small doses of valerian for 1 month. Adding nortriptyline to valerian caused a toxic delirium. She developed severe akathisia and became suicidal, then committed homicide after 3 days.

The outcome of the event 'Akathisia' was reported as 'resolved' and the outcome of the event 'Homicide, Suicidal ideation and Delirium' were reported as 'unknown' at the time of this report.

Case outcome: Unknown

The case is deemed serious. Medical Reviewer considered the case to be possibly related to suspect drug due to its temporal association as per WHO UMC system for standardized causality assessment.

F/U#1: 16-Mar-2012 (Significant)



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A follow up was received to the case with following significant informations as:

# Authors details were updated.

# Dechallenge for Nortriptyline (company suspect product) was updated to "Positive" from "Unknown"

# Following event (PT) was added

1) Drug interaction with outcome as 'Resolved'

# Outcome of the events (PT) "Homicide, Suicidal ideation and Delirium" were updated to "Resolved" from "Unknown"

As per follow up report,

Table 3. Information on subject's drug regimens, CYP 450 genotypes, criminal facts and outcomes for ten of those suffering violant akathisia

# Subject number: (b) (6)

# Age; 35

# Gender: Female

# Drug, dose and treatment duration: Nortriptyline (12.5 mg/day) superimposed on valerian

# Reason for treatment : Treated for distress due to husband's drinking

# Genotypes - # of null, diminished or ultrarapid metabolizer alleles: 2D6 \*4/\*41, 2C9 \*1/\*2, 2C19 \*1/\*17; One null allele, Two diminished alleles ,One ultrarapid allele

# Circumstances of crime: Killed (b) (6) daughter in toxic delirium after 3 days

# Outcome: Pleaded mental illness, misdiagnosed with schizophrenia and treated with more CYP450 substrates.

Recovered on withdrawal but more drugs are still being prescribed on Tribunal orders with near fatal consequences

'Subject (b) (6) (35-year-old female; genotypes: CYP2D6 \*4/\*41, CYP2C9 \*1/\*2, and CYP2C19 \*1/\*17) was prescribed a low dose of the 2D6-metabolized tricyclic antidepressant nortriptyline (12.5 mg/day) 3 days prior to committing homicide. She was severely impaired in metabolizing this drug owing to the 2D6 combination of \*4 (null allele) and \*41 (reduced activity allele). This subject also had reduced metabolism through 2C9 (\*1/\*2) and increased (ultrarapid) metabolism through 2C19 (\*1/\*17), although the significance of these genotypes for nortriptyline metabolism is unclear.

Subject (b) (6), in her own words:



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My husband was drinking. I took small doses of valerian for a month and had (b) (6). When I took nortriptyline, I immediately wanted to kill myself, talked myself out of it. I'd never had thoughts like that before. My husband was angry, shouting. I walked outside a lot, with palpitations, trouble breathing, and became more depressed. My smoking went up to 25 a day. no alcohol. I didn't sleep for two nights. dreamt. then slept maybe three hours. felt awful. I dreamt that (b) (6). I felt like a zombie. I believed I had to help my daughter. (b) (6). I picked up a knife and stabbed her and woke up. I was not myself. (b) (6). She said: (b) (6). "I realized what I'd done. (b) (6). (b) (6), but the pills started again and thoughts of killing myself returned.

Nortriptyline is extensively metabolized in the liver, primarily by hydroxylation. There is a strong correlation between total plasma clearance of nortriptyline and 2D6 enzyme activity. Reduced clearance resulting from this subject's 2D6 genotype alone would lead to a build up of serum nortriptyline, which has been shown to be associated with loss of efficacy, toxicity, and increased adversity in several studies. Nortriptyline is also significantly metabolized through 3A4 as an additional pathway, according to in vitro and in vivo data. In the case of severely reduced metabolism through 2D6, as in this subject, 3A4 would have been the major pathway for metabolism. However, the nortriptyline was superimposed on valerian, which has been shown to be a 3A4 inhibitor in vitro and to significantly increase the maximum serum levels of a 3A4 substrate in vivo. The addition of a substrate to an inhibitor is one drug-drug interaction scenario (Pattern 2), as described in Armstrong et al. The addition of nortriptyline to valerian immediately provoked a toxic delirium in this subject; she became akathisia and suicidal and 3 days later she committed the homicide.

Conclusion : A detailed history and mental-state examination in these subjects presented here can exclude functional mental illness (which still has no biological markers) and confirm neurotoxicity. Pharmacogenetic evidence can assist with the rediagnosis of the population that causes the increased demand for mental health services. Restoring them to normality will reduce that demand and associated costs by taking pressure off ambulances, hospitals, prisons, and forensic wards. Akathisia homicides have been defended as instances of involuntary intoxication both with and without genetic evidence. Some perpetrators (and victims) succeed in receiving damages from the manufacturers for failure to warn. The Innocence Project examined evidence from crimes that took place before DNA testing was available. Personalized medicine in health care can bring about corresponding personalized justice in clinics, tribunals, courts and morgues."

Case outcome: Resolved.

Ranbaxy medical reviewers comment :~



# FDA - Adverse Event Reporting System (FAERS)

FDACDER3094

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The case is deemed serious. Medical Reviewer considered the case to be possibly related to suspect drug due to its temporal association as per WHO UMC system for standardized causality assessment.

### Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

### Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

### Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

### Reporter Source:

**Study Report?:** No      **Sender Organization:** RANBAXY



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**Literature Text:** Lucire Y, Crotty. Antidepressant-induced Akathisia-related homicides associated with diminishing mutations in metabolizing genes of the CYP450 family. *Pharmacogenomics and Personalized Medicine*. 2011;4(1):65-81