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# The clinical heterogeneity of drug-induced myoclonus: an illustrated review

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**Abstract** A wide variety of drugs can cause myoclonus. To illustrate this, we first discuss two personally observed cases, one presenting with generalized, but facial-predominant, myoclonus that was induced by amantadine; and the other presenting with propriospinal myoclonus triggered by an antibiotic. We then review the literature on drugs that may cause myoclonus, extracting the corresponding clinical phenotype and suggested underlying pathophysiology. The most frequently reported classes of drugs causing myoclonus include opiates, antidepressants, antipsychotics, and antibiotics. The distribution of myoclonus ranges from focal to generalized, even amongst patients using the same drug, which suggests various neuro-anatomical generators. Possible underlying pathophysiological alterations involve serotonin, dopamine, GABA, and glutamate-related processes at various levels of the

neuraxis. The high number of cases of drug-induced myoclonus, together with their reported heterogeneous clinical characteristics, underscores the importance of considering drugs as a possible cause of myoclonus, regardless of its clinical characteristics.

**Keywords** Drug-induced myoclonus · Myoclonus/phenotype · Myoclonus/physiopathology

## Introduction

Myoclonus are involuntary sudden, brief, shock-like ‘jerky’ movements due to muscular contractions (‘positive myoclonus’) or sudden lapses of muscle contraction in active muscles (‘negative myoclonus’ or ‘asterixis’) [40, 44]. Myoclonus can be classified by distribution (focal, segmental, multifocal, and generalized) [75], by localization of the ‘pulse generator’ (cortical, subcortical, brainstem, spinal, or peripheral) [44], and by aetiology (physiological, essential, epileptic, symptomatic, and psychogenic) [44, 52]. In this paper, we review the phenomenon of drug-induced myoclonus, a subgroup of symptomatic myoclonus, with an emphasis on the clinical and pathophysiological heterogeneity of this phenomenon, which could mislead clinicians and result in insufficient consideration of drugs as the cause of myoclonus.

We first describe two personally observed cases of drug-induced myoclonus. Next, we present the results of our literature search on those drugs reported to cause myoclonus, including details of the corresponding clinical phenotype and, whenever available, data on the neuro-anatomical origins and pathophysiological processes.

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## Case description

### Case A

Patient A was a 79-year-old woman who developed her first ever epileptic seizure 2 days after the start of intravenous penicillin and ciprofloxacin prescribed for pneumonia. On neurological examination after the seizure she was alert but showed jerky movements of trunk, abdomen, and arms (particularly the right shoulder) more than of her legs that she could not suppress (video 1). The spread and temporal gradient of these jerks were particularly indicative of propriospinal myoclonus. EEG showed no epileptic phenomena, not even at the time when the movements occurred during recording. Antibiotic therapy was switched to claritromycin and ceftazidim, after which the myoclonus disappeared. The final diagnosis was that of ciprofloxacin and/or penicillin-induced propriospinal myoclonus.

### Case B

Patient B was a 66-year-old man who had been diagnosed 12 years previously with Parkinson's disease for which he took levodopa/benserazide 125 mg t.i.d. plus 125 mg b.i.d. as dispersible tablets, and ropinirole 6 mg b.i.d. His medical history reported a left-sided stereotactic thalamotomy because of a troublesome tremor of his right hand and a cervical disc herniation. Because of peak-dose dyskinesias and marked off periods during the night, amantadine was started and augmented to 100 mg t.i.d. Slow-release levodopa/benserazide ante noctum was added to the treatment regimen. One month after these treatment adjustments, the patient developed involuntary jerks through his whole body but predominantly in his face and neck, also severely affecting his speech. These jerks were not sensitive to stimuli and occurred mainly during action (both positive and negative) but were also present at rest. During walking, axial action myoclonus was apparent (video 2). The remaining examination showed an asymmetric hypokinetic-rigid syndrome, the severity of which was similar to prior examination. Suspecting drug-induced generalized myoclonus, amantadine was tapered off, and the myoclonus disappeared within 2 weeks.

## Methods

### Search strategy

We searched PubMed using the MeSH terms “Myoclonus/chemically induced”, “Myoclonus/etiology”, “Myoclonus/pharmacology”, “Myoclonus/physiology”, “Myoclonus/physiopathology”, “Drug-Related Side

Effects and Adverse Reactions”, and “Dyskinesia, Drug-Induced”. Only articles in English, published before September 2016, were reviewed for relevance.

## Results

Our literature search on drug-induced myoclonus mainly identified case reports and (mostly small) case series (the largest involving 32 patients). Table 1 summarizes the number of cases reported per subclass of drugs associated with myoclonus, the distribution of myoclonus, and one or two relevant references per category. The full table with all references considered (Table 2) is available as supplementary material. Almost all classes of drugs have been linked to myoclonus. The clinical phenotype covered the whole spectrum, from a focal to a generalized distribution. The presumed anatomic structures and neurotransmitters involved are suggested to differ per causative agent. Drug-induced myoclonus was usually reversible following withdrawal of the offending drug [10, 44], and only a single case of persistent myoclonus has been reported [75]. We here describe the characteristics of myoclonus caused by the four classes of drugs most often reported in relation to myoclonus (opiates, antidepressants, antipsychotics, and antibiotics) and by the group of drugs involved in our case B (NMDA antagonists).

### Opiates

Myoclonus may occur as a result of initial administration, change, or withdrawal of opiates [19, 32, 47]. Mainly generalized, but also multifocal and a single case of focal myoclonus have been described (Table 1, and supplementary Table 2). Opiate-related myoclonus occurs more frequently in patients concurrently treated with antidepressant, antipsychotic, antiemetic, or nonsteroidal anti-inflammatory drugs [47]. The precise pathophysiology remains poorly understood. A neuro-excitatory effect of opioid compounds and metabolites has been attributed to glutamate activation of *N*-methyl-D-aspartate (NMDA) receptors, glycine-mediated disinhibition of neural pathways at the cortical or spinal level, antagonism of gamma-aminobutyric acid (GABA) activity in the spinal cord, serotonergic and GABAergic pathways in the brainstem, and dopaminergic pathways in the basal ganglia [32].

### Antidepressants

Various classes of antidepressants have been associated with myoclonus (Table 1, and supplementary Table 2). Selective serotonin-reuptake inhibitors (SSRIs) can cause multifocal [30, 67] or generalized myoclonus [48, 64, 86].

**Table 1** Case reports and illustrative references upon medication-induced myoclonus

| Pharmacological class | Pharmacological subclass                                                                | Number of cases reported |        |           |             | Illustrative reference(s) |                            |   |
|-----------------------|-----------------------------------------------------------------------------------------|--------------------------|--------|-----------|-------------|---------------------------|----------------------------|---|
|                       |                                                                                         | All distributions        | Focal  | Segmental | Multifocal  | Generalized               | Distribution not described |   |
| Opiates               | Full agonists                                                                           | 105                      | 1 [47] | –         | 18 [32]     | 13 [19]                   | 73 [7, 8378]               | – |
|                       | Partial agonist–antagonist                                                              | 7                        | –      | –         | –           | –                         | 7 [7]                      | – |
| Antidepressants       | Selective serotonin-reuptake inhibitors (SSRIs)                                         | 44                       | –      | –         | 2 [30]      | 6 [86]                    | 36 [74]                    | – |
|                       | Tricyclic antidepressants (TCAs)                                                        | 55                       | 5 [54] | –         | 2 [20]      | 4 [68]                    | 44 [7, 8]                  | – |
|                       | Lithium                                                                                 | 10                       | –      | –         | 6 [11, 20]  | 2 [14]                    | 2 [7]                      | – |
|                       | Monoamine oxidase (MAO) inhibitors                                                      | 4                        | –      | –         | 1 [5]       | –                         | 3 [7]                      | – |
|                       | Serotonin-norepinephrine reuptake inhibitor (SNRI)                                      | 1                        | –      | –         | –           | 1 [18]                    | –                          | – |
|                       | Noradrenalin and dopamine reuptake inhibitors                                           | 1                        | 1 [31] | –         | –           | –                         | –                          | – |
| Antipsychotics        | Typical                                                                                 | 65                       | –      | –         | 56 [93]     | 1 [16]                    | 8 [7]                      | – |
|                       | Atypical                                                                                | 15                       | –      | –         | 5 [6]       | 3 [92]                    | 7 [7]                      | – |
| Antibiotics           | β-lactams                                                                               | 40                       | –      | –         | 3 [80]      | 3 [87]                    | 34 [7, 79]                 | – |
|                       | Quinolones                                                                              | 34                       | –      | –         | 2 [81]      | 2 [21]                    | 30 [7]                     | – |
|                       | Sulfonamides                                                                            | 3                        | –      | –         | 2 [41]      | 1 [58]                    | –                          | – |
|                       | Aminoglycosides                                                                         | 6                        | –      | –         | –           | 1 [75]                    | 5 [7]                      | – |
| Anxiolytics           | Benzodiazepines                                                                         | 66                       | –      | –         | 7 [51]      | –                         | 59 [7]                     | – |
|                       | Gabapentin                                                                              | 27                       | 3 [4]  | –         | 17 [4, 101] | 3 [77, 101]               | 4 [7]                      | – |
| Anti-epileptics       | Pregabalin                                                                              | 9                        | 1 [35] | –         | 8 [63]      | –                         | –                          | – |
|                       | Valproic acid                                                                           | 10                       | –      | –         | –           | 1 [98]                    | 9 [1, 7]                   | – |
|                       | Lamotrigine                                                                             | 7                        | –      | –         | 3 [23]      | 1 [13]                    | 3 [74]                     | – |
|                       | Carbamazepine                                                                           | 5                        | 1 [50] | –         | –           | –                         | 4 [7, 27]                  | – |
|                       | Phenytoine                                                                              | 4                        | –      | –         | –           | 2 [17]                    | 2 [7]                      | – |
|                       | Topiramate                                                                              | 4                        | 2 [45] | –         | 1 [3]       | 1 [64]                    | –                          | – |
|                       | Phenobarbital                                                                           | 2                        | –      | –         | –           | –                         | 2 [7]                      | – |
|                       | Vigabatrin                                                                              | 2                        | –      | –         | 2 [62]      | –                         | –                          | – |
| Anti-parkinsonians    | Clobazam                                                                                | 1                        | –      | –         | –           | –                         | 1 [27]                     | – |
|                       | L-dopa                                                                                  | 28                       | –      | –         | –           | –                         | 28 [7, 43, 90]             | – |
|                       | Dopamine agonists                                                                       | 8                        | –      | –         | –           | –                         | 8 [7, 90]                  | – |
|                       | Non-competitive (NMDA)-glutamatergic-antagonist (amantadine) (also see 'anti-dementia') | 10                       | 2 [31] | –         | –           | 1 [96]                    | 7 [55]                     | – |
|                       | COMT inhibitors                                                                         | 1                        | –      | –         | –           | –                         | 1 [7]                      | – |
|                       | MAO-inhibitors                                                                          | 1                        | –      | –         | –           | –                         | 1 [7]                      | – |
| Anesthetics           | General anesthetics                                                                     | 42                       | 1 [89] | 15 [97]   | 8 [97]      | 7 [97, 46]                | 11 [7]                     | – |
|                       | Local anesthetics                                                                       | 4                        | –      | –         | 4 [2]       | –                         | –                          | – |

Table 1 continued

| Pharmacological class | Pharmacological subclass                                                                          | Number of cases reported |        |           |            |             | Illustrative reference(s)  |  |
|-----------------------|---------------------------------------------------------------------------------------------------|--------------------------|--------|-----------|------------|-------------|----------------------------|--|
|                       |                                                                                                   | All distributions        | Focal  | Segmental | Multifocal | Generalized | Distribution not described |  |
| Anti-dementia         | Cholinesterase inhibitors                                                                         | 18                       | –      | –         | –          | –           | 18 [7]                     |  |
|                       | Non-competitive (NMDA)-glutamate receptor-antagonist (memantine)<br>(also see anti-parkinsonians) | 9                        | –      | 1 [69]    | –          | 3 [60]      | 5 [7, 66]                  |  |
| Cytostatics           | Ifosfamide                                                                                        | 5                        | –      | –         | 1 [56]     | 4 [76]      | –                          |  |
|                       | Prednimustine                                                                                     | 4                        | –      | –         | 3 [53, 59] | 1 [53]      | –                          |  |
|                       | Chlorambucil                                                                                      | 2                        | –      | –         | 1 [95]     | –           | 1 [95]                     |  |
| Others                | Anti-emetics                                                                                      | 23                       | 1 [36] | 1 [61]    | 2 [12]     | –           | 19 [7]                     |  |
|                       | Anti-arrhythmics                                                                                  | 5                        | –      | –         | 3 [91]     | 1 [84]      | 1 [7]                      |  |
|                       | Vitamins                                                                                          | 5                        | –      | –         | 4 [99]     | 1 [65]      | –                          |  |
|                       | Anti-hypertensives                                                                                | 2                        | –      | –         | 2 [88]     | –           | –                          |  |
|                       | Contrast agents                                                                                   | 3                        | 1 [24] | –         | 2 [9]      | –           | –                          |  |
|                       | Immunomodulating drugs                                                                            | 2                        | –      | –         | 1 [22]     | –           | 1 [7]                      |  |
|                       | Anti-fibrinolytic agents                                                                          | 1                        | –      | –         | 1 [34]     | –           | –                          |  |
|                       | Anti-histamines                                                                                   | 1                        | –      | –         | –          | 1 [37]      | –                          |  |
|                       | Anti-hypotensives                                                                                 | 1                        | –      | –         | –          | –           | 1 [94]                     |  |
|                       | Anti-tussives                                                                                     | 1                        | –      | –         | –          | 1 [82]      | –                          |  |
|                       | Adrenergic bronchodilators                                                                        | 3                        | –      | –         | 3 [57]     | –           | –                          |  |
|                       | NSAID                                                                                             | 1                        | –      | –         | –          | –           | 1 [7]                      |  |
|                       | Anti-viral agents                                                                                 | 1                        | –      | –         | 1 [28]     | –           | –                          |  |
|                       | Anti-malaria prophylaxis                                                                          | 1                        | –      | –         | 1 [39]     | –           | –                          |  |

Classes and subclasses of drugs described to cause drug-induced myoclonus. References were sorted to distribution of myoclonus. The numbers of reported cases of drug-induced myoclonus are listed. One or two illustrative reference(s) per distribution is/are listed in superscript

– No studies describing myoclonus with this distribution, for this class of drugs. The references used to count the number of cases reported are listed in Table 2 available as ‘supplementary material’

Tricyclic antidepressants (TCAs) can cause either focal (especially jaw) [26, 54], multifocal [20, 42], and generalized [14, 49, 68, 98] myoclonus. Lithium has been observed to cause multifocal [11, 20] and generalized [14] myoclonus. An EEG transient over the contralateral sensorimotor region preceding the myoclonus suggested a cortical origin of myoclonus in patients treated with a TCA [20] or lithium [11]. Serotonergic mechanisms are probably involved in the generation of antidepressant-induced myoclonus [30]. While SSRIs increase serotonin levels in the synaptic cleft, TCAs increase serotonin activity, and lithium facilitates the presynaptic release of serotonin [20]. A combination of two serotonergic active drugs, such as a TCA and lithium, appears more likely to cause myoclonus than a single drug [14, 20].

### Antipsychotics

Classic antipsychotics, including haloperidol, have been reported to cause multifocal myoclonus of both arms, sensitive to posture [25, 85]; of limbs and of the face [16]; and of the trunk and limbs [93]. Atypical antipsychotics, including quetiapine and olanzapine, can cause both multifocal [33, 72] and generalized [29, 73, 92] myoclonus. The exact pathogenesis of antipsychotic-induced myoclonus has not yet been unraveled, but involvement of serotonergic [16, 72], dopaminergic [93], and GABA-ergic [92] mechanisms have all been suggested.

### Antibiotics

Antibiotic-induced myoclonus mainly occurs in association with high or toxic doses of antibiotics and/or underlying renal disease [75]. It is commonly accompanied by other symptoms, such as altered mental state, seizures (similar to our case A), aphasia, chorea, and skin rash [75]. Myoclonus due to  $\beta$ -lactam antibiotics clinically varies from subtle peri-ocular twitching to generalized myoclonus [75]. Myoclonus due to quinolones can be generalized [21, 38] or multifocal [81]. It is hypothesized that  $\beta$ -lactam antibiotics selectively antagonize [75] and quinolones completely inhibit [71] gamma aminobutyric acid (GABA) receptors, decreasing their inhibitory activity at nerve terminals, thus inducing a hyperexcitable neuronal state of the central nervous system that triggers myoclonus. Sulfonamides have been associated with multifocal and generalized myoclonus. A causative role of altered dopamine metabolism due to inhibition of dihydrofolate reductase [15] as well as increased phenylalanine levels due to the inhibition of phenylalanine metabolism have been proposed [41]. Multifocal myoclonus that is due to aminoglycosides has been attributed to NMDA receptor activation and subsequent excitotoxicity.

### NMDA antagonists

Myoclonus due to *N*-methyl-D-aspartate (NMDA) receptor antagonists has rarely been reported. Amantadine has been shown to reduce levodopa-induced dyskinesias [100] but paradoxically has also been reported to induce jaw myoclonus in two patients [31, 70] and generalized myoclonus in four patients [55, 96]. In addition, memantine gave rise to myoclonus in patients with dementia [58, 60, 66]. The mechanism underlying amantadine and memantine induced myoclonus remains unclear, but might involve altered levels of dopamine, serotonin, and/or glutamate release [55, 96].

### Conclusion

A French pharmacovigilance database study [7], registering all compulsorily reported adverse drug reactions in France, reported an incidence of drug-induced myoclonus of 0.2% (423/185,634 reported adverse events over a 20-year period), which might be an underestimation due to underreporting [7]. Our literature survey is not suitable to extract epidemiological data, but the large number of case reports that we identified does suggest that drug-induced myoclonus is not an uncommon phenomenon in movement disorder consultations. Of course, we cannot offer certainty about causality for the observed associations between drugs and myoclonus, which is inherent to a literature review of case reports and case series. However, in many cases, myoclonus appeared shortly after the prescription of a new (and presumably causally involved) drug, and disappeared again readily after this same drug was stopped, suggesting a causal relationship.

Our survey—as well as the French pharmacovigilance database study—found that the most important groups of drugs with links to myoclonus are: opiates, antidepressants, antipsychotic drugs, and antibiotics. However, drug-induced myoclonus may also be caused by a wide variety of other drugs. Drug-induced myoclonus is usually reversible upon discontinuation of the offending drug, and this stresses the importance of making the correct diagnosis of drug-induced myoclonus. Importantly, the phenomenology of the myoclonus can vary within a group of drugs and even for one particular drug, suggesting that the neuro-anatomical generator varies. From a clinical perspective, this also means that drugs as a cause cannot be discarded based solely on clinical myoclonus characteristics. The precise cellular and neurochemical alterations that make a certain drug cause myoclonus remain largely unclear and therefore need further study.

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#### Compliance with ethical standards

**Conflicts of interest** S Janssen: no conflicts of interest to declare. BP van de Warrenburg: no conflicts of interest to declare. BR Bloem: no conflicts of interest to declare.

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## References

1. Aguglia U, Gambardella A, Zappia M, Valentino P, Quattrone A (1995) Negative myoclonus during valproate-related stupor. Neurophysiological evidence of a cortical non-epileptic origin. *Electroencephalogr Clin Neurophysiol* 94:103–108
2. Alfa JA, Bamgbade OA (2008) Acute myoclonus following spinal anaesthesia. *Eur J Anaesthesiol* 25:256–257
3. Alonso-Navarro H, Jimenez-Jimenez FJ (2006) Reversible tremor, myoclonus, and fasciculations associated with topiramate use for migraine. *Clin Neuropharmacol* 29:157–159
4. Asconape J, Diedrich A, DellaBadia J (2000) Myoclonus associated with the use of gabapentin. *Epilepsia* 41:479–481
5. Askenasy JJ, Yahr MD (1988) Is monoamine oxidase inhibitor induced myoclonus serotonergically mediated? *J Neural Transm* 72:67–76
6. Barak Y, Levine J, Weisz R (1996) Clozapine-induced myoclonus: two case reports. *J Clin Psychopharmacol* 16:339–340
7. Brefel-Courbon C, Gardette V, Ory F, Montastruc JL (2006) Drug-induced myoclonus: a French pharmacovigilance database study. *Neurophysiol Clin* 36:333–336
8. Casas M, Garcia-Ribera C, Alvarez E, Udina C, Queraltó JM, Grau JM (1987) Myoclonic movements as a side-effect of treatment with therapeutic doses of clomipramine. *Int Clin Psychopharmacol* 2:333–336
9. Casazza M, Bracchi M, Girotti F (1985) Spinal myoclonus and clinical worsening after intravenous contrast medium in a patient with spinal arteriovenous malformation. *AJNR Am J Neuroradiol* 6:965–966
10. Caviness JN, Brown P (2004) Myoclonus: current concepts and recent advances. *Lancet Neurol* 3:598–607
11. Caviness JN, Evidente VG (2003) Cortical myoclonus during lithium exposure. *Arch Neurol* 60:401–404
12. Chaw SH, Chan L, Lee PK, Bakar JA, Rasiyah R, Foo LL (2016) Prolonged drug-induced myoclonus: is it related to palonose-tron? *J Anesth* 30(6):1063–1066
13. Crespel A, Genton P, Berramdane M, Coubes P, Monicard C, Baldy-Moulinier M, Gelisse P (2005) Lamotrigine associated with exacerbation or de novo myoclonus in idiopathic generalized epilepsies. *Neurology* 65:762–764
14. Devanand DP, Sackeim HA, Brown RP (1988) Myoclonus during combined tricyclic antidepressant and lithium treatment. *J Clin Psychopharmacol* 8:446–447
15. Dib EG, Bernstein S, Benesch C (2004) Multifocal myoclonus induced by trimethoprim-sulfamethoxazole therapy in a patient with nocardia infection. *N Engl J Med* 350:88–89
16. Dominguez C, Benito-Leon J, Bermejo-Pareja F (2009) Multifocal myoclonus induced by haloperidol. *Neurol Sci* 30:385–386
17. Duarte J, Sempere AP, Cabezas MC, Marcos J, Claveria LE (1996) Postural myoclonus induced by phenytoin. *Clin Neuropharmacol* 19:536–538
18. Dutra LA, Pedroso JL, Felix EP, Barsottini OG (2008) Venlafaxine induced-myoclonus in a patient with mixed dementia. *Arq Neuropsiquiatr* 66:894–895
19. Essandoh S, Sakae M, Miller J, Glare PA (2010) A cautionary tale from critical care: resolution of myoclonus after fentanyl rotation to hydromorphone. *J Pain Symptom Manage* 40:e4–6
20. Evidente VG, Caviness JN (1999) Focal cortical transient preceding myoclonus during lithium and tricyclic antidepressant therapy. *Neurology* 52:211–213
21. Farrington J, Stoudemire A, Tierney J (1995) The role of ciprofloxacin in a patient with delirium due to multiple etiologies. *Gen Hosp Psychiatry* 17:47–53
22. Ferbert A, Biniek R, Kindler J, Maurin N (1993) Myoclonus and tremor induced acutely by administration of tumor necrosis factor in a patient with Ehlers-Danlos syndrome. *Mov Disord* 8:232–233
23. Fernandez Corcuera P, Pomarol E, Amann B, McKenna P (2008) Myoclonus provoked by lamotrigine in a bipolar patient. *J Clin Psychopharmacol* 28:248–249
24. Finsterer J, Lubec D, Verlicchi A, Samec P (1998) Facial myocloni and stroke as late sequelae of metrizamide myelography. *J Neuropsychiatry Clin Neurosci* 10:472–473
25. Fukuzako H, Tominaga H, Izumi K, Koja T, Nomoto M, Hokazono Y, Kamei K, Fujii H, Fukuda T, Matsumoto K (1990) Postural myoclonus associated with long-term administration of neuroleptics in schizophrenic patients. *Biol Psychiatry* 27:1116–1126
26. Garvey MJ, Tollefson GD (1987) Occurrence of myoclonus in patients treated with cyclic antidepressants. *Arch Gen Psychiatry* 44:269–272
27. Genton P, Nguyen VH, Mesdjian E (1998) Carbamazepine intoxication with negative myoclonus after the addition of clonazepam. *Epilepsia* 39:1115–1118
28. Gentry JL 3rd, Peterson C (2015) Death delusions and myoclonus: acyclovir toxicity. *Am J Med* 128:692–694
29. George M, Haasz M, Coronado A, Salhanick S, Korbel L, Kitzmiller JP (2013) Acute dyskinesia, myoclonus, and akathisia in an adolescent male abusing quetiapine via nasal insufflation: a case study. *BMC Pediatr* 13:187
30. Ghaziuddin N, Iqbal A, Khetarpal S (2001) Myoclonus during prolonged treatment with sertraline in an adolescent patient. *J Child Adolesc Psychopharmacol* 11:199–202
31. Gupta A, Lang AE (2010) Drug-induced cranial myoclonus. *Mov Disord* 25:2264–2265
32. Han PK, Arnold R, Bond G, Janson D, Abu-Elmagd K (2002) Myoclonus secondary to withdrawal from transdermal fentanyl: case report and literature review. *J Pain Symptom Manage* 23:66–72
33. Horga G, Horga A, Baeza I, Castro-Fornieles J, Lazaro L, Pons A (2010) Drug-induced speech dysfluency and myoclonus preceding generalized tonic-clonic seizures in an adolescent male with schizophrenia. *J Child Adolesc Psychopharmacol* 20:233–234

34. Hui AC, Wong TY, Chow KM, Szeto CC (2003) Multifocal myoclonus secondary to tranexamic acid. *J Neurol Neurosurg Psychiatry* 74:547
35. Huppertz HJ, Feuerstein TJ, Schulze-Bonhage A (2001) Myoclonus in epilepsy patients with anticonvulsive add-on therapy with pregabalin. *Epilepsia* 42:790–792
36. Immovilli P, Rota E, Morelli N, Iafelice I, Magnacavallo A, Guidetti D (2015) Metoclopramide-induced facial and palatopharyngeal myoclonus. *Neurology* 84:1284
37. Irioka T, Machida A, Yokota T, Mizusawa H (2008) Antihistamine-associated myoclonus: a case report. *Mov Disord* 23:1615–1616
38. Jayathissa S, Woolley M, Ganasegaram M, Holden J, Cu E (2010) Myoclonus and delirium associated with ciprofloxacin. *Age Ageing* 39:762
39. Jimenez-Huete A, Gil-Nagel A, Franch O (2002) Multifocal myoclonus associated with mefloquine chemoprophylaxis. *Clin Neuropharmacol* 25:243
40. Jimenez-Jimenez FJ, Puertas I, de Toledo-Heras M (2004) Drug-induced myoclonus: frequency, mechanisms and management. *CNS Drugs* 18:93–104
41. Jundt F, Lempert T, Dorken B, Pezzutto A (2004) Trimethoprim-sulfamethoxazole exacerbates posthypoxic action myoclonus in a patient with suspicion of *Pneumocystis jiroveci* infection. *Infection* 32:176–178
42. Kettl P, DePaulo JR Jr (1983) Maprotiline-induced myoclonus. *J Clin Psychopharmacol* 3:264–265
43. Klawans HL, D'Amico DJ, Patel BC (1975) Behavioral supersensitivity to 5-hydroxytryptophan induced by chronic methysergide pretreatment. *Psychopharmacologia* 44:297–300
44. Kojovic M, Cordivari C, Bhatia K (2011) Myoclonic disorders: a practical approach for diagnosis and treatment. *Ther Adv Neurol Disord* 4:47–62
45. Kutluay E, Pakoz B, Beydoun A (2007) Reversible facial myoclonus with topiramate therapy for epilepsy. *Epilepsia* 48:2001–2002
46. Laughlin TP, Newberg LA (1985) Prolonged myoclonus after etomidate anesthesia. *Anesth Analg* 64:80–82
47. Lauterbach EC (1999) Hiccup and apparent myoclonus after hydrocodone: review of the opiate-related hiccup and myoclonus literature. *Clin Neuropharmacol* 22:87–92
48. Lauterbach EC (1994) Reversible intermittent rhythmic myoclonus with fluoxetine in presumed Pick's disease. *Mov Disord* 9:343–346
49. Lippmann S, Moskovitz R, O'Tuama L (1977) Tricyclic-induced myoclonus. *Am J Psychiatry* 134:90–91
50. Magaouda A, Di Rosa G (2012) Carbamazepine-induced non-epileptic myoclonus and tic-like movements. *Epileptic Disord* 14:172–173
51. Magny JF, d'Allest AM, Nedelcoux H, Zupan V, Dehan M (1994) Midazolam and myoclonus in neonate. *Eur J Pediatr* 153:389–390
52. Marsden CD, Hallett M, Fahn S (1982) The nosology and pathophysiology of myoclonus. *Movement Disorders*. Butterworths, London, pp 196–248
53. Martin M, Diaz-Rubio E, Casado A, Valverde JJ, Garcia Urra D, Lopez-Martin JA, Rodriguez-Lescure A (1994) Prednimustine-induced myoclonus—a report of three cases. *Acta Oncol* 33:81–82
54. Masand P (1992) Desipramine-induced oral-pharyngeal disturbances: stuttering and jaw myoclonus. *J Clin Psychopharmacol* 12:444–445
55. Matsunaga K, Uozumi T, Qingrui L, Hashimoto T, Tsuji S (2001) Amantadine-induced cortical myoclonus. *Neurology* 56:279–280
56. Meyer T, Ludolph AC, Munch C (2002) Ifosfamide encephalopathy presenting with asterixis. *J Neurol Sci* 199:85–88
57. Micheli F, Cersosimo MG, Scorticati MC, Velez M, Gonzalez S (2000) Myoclonus secondary to albuterol (salbutamol) instillation. *Neurology* 54:2022–2023
58. Moellentin D, Picone C, Leadbetter E (2008) Memantine-induced myoclonus and delirium exacerbated by trimethoprim. *Ann Pharmacother* 42:443–447
59. Monnerat C, Gander M, Leyvraz S (1997) A rare case of prednimustine-induced myoclonus. *J Natl Cancer Inst* 89:173–174
60. Murgai AA, LeDoux MS (2015) Memantine-induced Myoclonus in a Patient with Alzheimer Disease. *Tremor and other hyperkinetic movements* 5:337
61. Nampiaparampil D, Oruc NE (2006) Metoclopramide-induced palatopharyngeal myoclonus. *Mov Disord* 21:2028–2029
62. Neufeld MY, Vishnevska S (1995) Vigabatrin and multifocal myoclonus in adults with partial seizures. *Clin Neuropharmacol* 18:280–283
63. Olszewska DA, Chalissery AJ, Williams J, Lynch T, Smyth S (2015) Speech myoclonus due to probable pregabalin adverse drug-reaction. *Parkinsonism Relat Disord* 21:823–824
64. Oulis P, Potagas C, Masdrakis VG, Thomopoulos Y, Kouzoupis AV, Soldatos CR (2008) Reversible tremor and myoclonus associated with topiramate-fluvoxamine coadministration. *Clin Neuropharmacol* 31:366–367
65. Ozer EA, Turker M, Bakiler AR, Yaprak I, Ozturk C (2001) Involuntary movements in infantile cobalamin deficiency appearing after treatment. *Pediatr Neurol* 25:81–83
66. Papageorgiou SG, Kontaxis T, Antelli A, Kalfakis N (2007) Exacerbation of myoclonus by memantine in a patient with Alzheimer disease. *J Clin Psychopharmacol* 27:407–408
67. Patel HC, Bruza D, Yeragani V (1988) Myoclonus with trazodone. *J Clin Psychopharmacol* 8:152
68. Patterson JF (1990) Myoclonus caused by a tricyclic antidepressant. *South Med J* 83:463–465
69. Pei LJ, Tianzhi IL, Lim WS (2015) Memantine-induced myoclonus precipitated by renal impairment and drug interactions. *J Am Geriatr Soc* 63:2643–2644
70. Pfeiffer RF (1996) Amantadine-induced “vocal” myoclonus. *Mov Disord* 11:104–106
71. Post B, Koelman JH, Tijssen MA (2004) Propriospinal myoclonus after treatment with ciprofloxacin. *Mov Disord* 19:595–597
72. Prahara SK, Venkatesh BG, Sarkhel S, Zia-ul-Haq M, Sinha VK (2010) Clozapine-induced myoclonus: a case study and brief review. *Prog Neuropsychopharmacol Biol Psychiatry* 34:242–243
73. Rosen JB, Milstein MJ, Haut SR (2012) Olanzapine-associated myoclonus. *Epilepsy Res* 98:247–250
74. Rosenhagen MC, Schmidt U, Weber F, Steiger A (2006) Combination therapy of lamotrigine and escitalopram may cause myoclonus. *J Clin Psychopharmacol* 26:346–347
75. Sarva H, Panichpisal K (2012) Gentamicin-induced myoclonus: a case report and literature review of antibiotics-induced myoclonus. *Neurologist* 18:385–388
76. Savica R, Rabinstein AA, Josephs KA (2011) Ifosfamide associated myoclonus-encephalopathy syndrome. *J Neurol* 258:1729–1731
77. Shea YF, Mok MM, Chang RS (2014) Gabapentin-induced myoclonus in an elderly with end-stage renal failure. *Journal of the Formosan Medical Association* =. *Taiwan yi zhi* 113:660–661
78. Sjogren P, Thunedborg LP, Christrup L, Hansen SH, Franks J (1998) Is development of hyperalgesia, allodynia and myoclonus related to morphine metabolism during long-term administration? Six case histories. *Acta Anaesthesiol Scand* 42:1070–1075



79. Sonck J, Laureys G, Verbeelen D (2008) The neurotoxicity and safety of treatment with cefepime in patients with renal failure. *Nephrol Dial Transplant* 23:966–970
80. Spina Silva T, Dal-Pra Ducci R, Zorzetto FP, Braatz VL, de Paola L, Kowacs PA (2014) Meropenem-induced myoclonus: a case report. *Seizure* 23:912–914
81. Striano P, Zara F, Coppola A, Ciampa C, Pezzella M, Striano S (2007) Epileptic myoclonus as ciprofloxacin-associated adverse effect. *Mov Disord* 22:1675–1676
82. Tanaka A, Nagamatsu T, Yamaguchi M, Nomura A, Nagura F, Maeda K, Tomino T, Watanabe T, Shimizu H, Fujita Y, Ito Y (2011) Myoclonus after dextromethorphan administration in peritoneal dialysis. *Ann Pharmacother* 45:e1
83. Thwaites D, McCann S, Broderick P (2004) Hydromorphone neuroexcitation. *J Palliat Med* 7:545–550
84. Ting SM, Lee D, Maclean D, Sheerin NS (2008) Paranoid psychosis and myoclonus: flecainide toxicity in renal failure. *Cardiology* 111:83–86
85. Tominaga H, Fukuzako H, Izumi K, Kojia T, Fukuda T, Fujii H, Matsumoto K, Sonoda H, Imamura K (1987) Tardive myoclonus. *Lancet* 1:322
86. Tremolizzo L, Fermi S, Fusco ML, Susani E, Frigo M, Piolti R, Ferrarese C, Appollonio I (2011) Generalized action myoclonus associated with escitalopram in a patient with mixed dementia. *J Clin Psychopharmacol* 31:394–395
87. Uchihara T, Tsukagoshi H (1988) Myoclonic activity associated with cefmetazole, with a review of neurotoxicity of cephalosporins. *Clin Neurol Neurosurg* 90:369–371
88. Vadlamudi L, Wijidicks EF (2002) Multifocal myoclonus due to verapamil overdose. *Neurology* 58:984
89. Van Keulen SG, Burton JH (2003) Myoclonus associated with etomidate for ED procedural sedation and analgesia. *Am J Emerg Med* 21:556–558
90. Vardi J, Glaubman H, Rabey JM, Streifler M (1978) Myoclonic attacks induced by L-dopa and bromocriptin in Parkinson patients: a sleep EEG study. *J Neurol* 218:35–42
91. Velasco SL, Sierra-Hidalgo F, Rodriguez RM, Guerreo AJ, Morales JR (2014) Flecainide-induced myoclonus. *Clin Neuropharmacol* 37:65–66
92. Velayudhan L, Kirchner V (2005) Quetiapine-induced myoclonus. *Int Clin Psychopharmacol* 20:119–120
93. Vural A, Tezer FI (2012) Myoclonus induced by haloperidol in the intensive care unit. *J Neuropsychiatry Clin Neurosci* 24:E41
94. Wierre L, Decaudin B, Barsumau J, Vairon MX, Horrent S, Odou P, Azar R (2004) Dobutamine-induced myoclonia in severe renal failure. *Nephrol Dial Transplant* 19:1336–1337
95. Wyllie AR, Bayliff CD, Kovacs MJ (1997) Myoclonus due to chlorambucil in two adults with lymphoma. *Ann Pharmacother* 31:171–174
96. Yarnall AJ, Burn DJ (2012) Amantadine-induced myoclonus in a patient with progressive supranuclear palsy. *Age Ageing* 41:695–696
97. Yates AM, Wolfson AB, Shum L, Kehrl T (2013) A descriptive study of myoclonus associated with etomidate procedural sedation in the ED. *Am J Emerg Med* 31:852–854
98. Yoon JH, Lee PH, Yong SW, Park HY, Lim TS, Choi JY (2008) Movement disorders at a university hospital emergency room. An analysis of clinical pattern and etiology. *J Neurol* 255:745–749
99. Zanus C, Alberini E, Costa P, Colonna F, Zennaro F, Carrozzini M (2012) Involuntary movements after correction of vitamin B12 deficiency: a video-case report. *Epileptic Disord* 14:174–180
100. Zesiewicz TA, Sullivan KL, Hauser RA (2007) Levodopa-induced dyskinesia in Parkinson's disease: epidemiology, etiology, and treatment. *Curr Neurol Neurosci Rep* 7:302–310
101. Zhang C, Glenn DG, Bell WL, O'Donovan CA (2005) Gabapentin-induced myoclonus in end-stage renal disease. *Epilepsia* 46:156–158