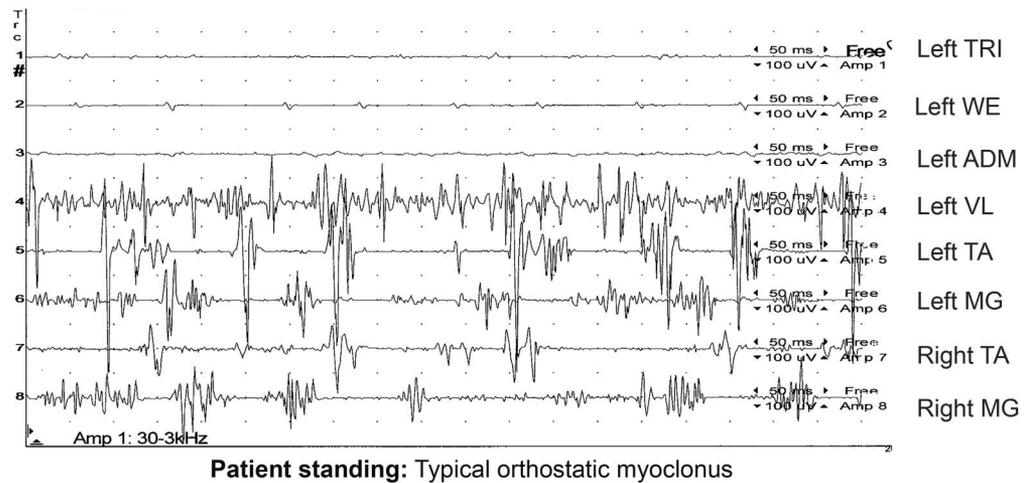


Figure Surface EMG recordings



**Abbreviations:** TRI = Triceps, WE = Wrist extensors, ADM = Adjector digiti minimi, VL = Vastus lateralis, TA = Tibialis anterior, MG = Medical gastrocnemius

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#### ANTIBIOTIC-ASSOCIATED ENCEPHALOPATHY

**Emmanuel Stip, Montreal:** Bhattacharyya et al. described a type II antibiotic-associated encephalopathy (AAE) where macrolides, among others, were involved.<sup>1</sup> The authors suggested that “type 2 AAE closely resemble[d] drug-induced psychotic syndromes caused by perturbations of the D2 dopamine and NMDA glutamate receptors.”<sup>1</sup> Where was the evidence of such a mechanism found? Additionally, penetration of clarithromycin into the CSF and brain tissue of a healthy animal is relatively low or absent. It is only when the blood–brain barrier is compromised that CNS concentrations might be rarely detectable.

Studies of neurotoxic effects with macrolides are limited. For instance, Bhattacharyya et al. documented 44 cases with clarithromycin, of which 23% (n = 10) noted a psychiatric history and 59% (n = 26) presented psychosis as a clinical feature.<sup>1</sup> Several fluoroquinolones enter the CNS readily and are valuable for the treatment of CNS infection contrary to macrolides, which have a high molecular mass and an affinity for P-glycoprotein. For procaine penicillin the case is simple: procaine is similar to cocaine.<sup>2</sup>

**Author Response: R. Ryan Darby, Cambridge, MA; Shamik Bhattacharyya, Aaron L. Berkowitz, Boston:** We appreciate Dr. Stip’s comments regarding the mechanism of type II AAE, characterized clinically by the predominance of psychosis.<sup>1</sup> As discussed in our review, and noted by Dr. Stip, procaine is chemically similar to cocaine and increases synaptic concentrations

of dopamine in rats,<sup>3</sup> suggesting a plausible mechanism for procaine penicillin-induced psychosis. Less evidence exists for the mechanism of fluoroquinolone-induced psychosis, although, as mentioned in our review, fluoroquinolones may alter dopamine levels or NMDA receptor activity.<sup>4,5</sup>

Dr. Stip correctly points out that there is no clear evidence to link macrolides to altered dopamine levels or NMDA receptor activity. Dr. Stip additionally argues that macrolides have poor CSF penetration because these drugs are highly lipophilic, large, and actively transported out of the brain by P-glycoproteins,<sup>2</sup> limiting the opportunity for direct neurotoxic effects. Conversely, clarithromycin is shown to have adequate CSF penetration. Furthermore, reduced clinical utility in treating CNS infections is due to reduced bactericidal activity of macrolides within the CSF, not low CSF penetration.<sup>6</sup>

We agree with Dr. Stip that the mechanism linking macrolides to psychosis is an area that merits further investigation.

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