Review Article

The Link Between Amitriptyline and Movement Disorders: Clinical Profile and Outcome

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Abstract

Introduction: Amitriptyline (AMT) is a tricyclic antidepressant. In this review, we evaluate the clinical and epidemiological profile, pathological mechanisms and management of AMT-associated movement disorders. Materials and Methods: A search for relevant reports in 6 databases was performed. Studies that reported patients developed only ataxia or tremor after AMT use were excluded. Results: A total of 48 reports on 200 cases were found. AMT-associated movement disorders included myoclonus (n = 26), dyskinesia (n = 11), dystonia (n = 8), stutter (n = 5), akathisia (n = 3) and restless legs syndrome (n = 1). For less well-defined cases, 99 patients had dyskinesia, 19 had psychomotor disturbances, 3 had myoclonus, 11 had dystonia, 12 had Parkinsonism and 1 each had akathisia and extrapyramidal symptoms. Mean and standard deviation (SD) and median ages were 45.40 years (SD 16.78) and 40 years (range 3.7–82 years), respectively. Over half were women (58.13%) and the most common indication was depression. Mean and median AMT doses were 126 mg (SD 128.76) and 75 mg (range 15–800 mg), respectively. In 68% of patients, onset of movement disorders was <1 month; time from AMT withdrawal to complete recovery was <1 month in 70% of cases. A weak negative linear correlation (r = −0.0904) was found between onset of movement disorders and AMT dose. AMT withdrawal was the most common treatment. Conclusion: Amitriptyline is associated with various movement disorders, particularly myoclonus, dystonia and dyskinesias. Stutters and restless legs syndrome are some of the less common associations.

Key words: Akathisia, Drug-induced, Dyskinesia, Dystonia, Myoclonus

Introduction

Amitriptyline (AMT) is classified as a tricyclic antidepressant (TCA). The development of AMT (Fig. 1) began in the mid-1950s after 2 American scientists, F Häfliger and Walter Schindler, serendipitously synthesised imipramine, the first TCA, when they replaced phenothiazine sulfur with ethylene in an attempt to develop a new antipsychotic drug.1 The Swiss psychiatrist, Roland Kuhn, had studied imipramine in various psychiatric disorders, and he noted that depressive patients experienced good improvement in their quality of life after they were given imipramine.2 His finding had since been confirmed by results from 60 studies.

Three years later, AMT was developed as a second TCA after the chemical structure of imipramine was modified with the substitution of C=CH with N-CH.3 In April 1961, the United States (US) Food and Drug Administration (FDA) approved AMT (Elavil®, MK-230) for the treatment of depression.4 In the following year, AMT was approved in the United Kingdom. 3 It is noteworthy that AMT is consistently ranked among the top 100 medications in the US after the FDA began to publish reports on the most frequently prescribed drugs in the country; it was ranked 54th in 1995, 40th in 2002 and 88th in 2016.3,5

To date, AMT is only approved for the treatment of depression. However, it has been used to treat other
conditions including anxiety, diabetic neuropathy, eating disorders, fibromyalgia, insomnia, irritable bowel syndrome, migraine prophylaxis, postherpetic neuralgia, post-traumatic stress disorder and sialorrhea. After oral administration, AMT is easily absorbed into the gastrointestinal tract before it is metabolised in the liver by the cytochrome P450 2C19 (CYP2C19) to become nortriptyline (NT). NT, in turn, is metabolised by CYP2D6 to become hydroxynortriptyline, which is the most abundant metabolite found in humans. Although a clear description of the metabolic pathway is lacking, studies of NT had found traces of AMT which strengthened the belief that AMT could be metabolised to become NT and vice versa.

In 2017, Banks et al. reported that AMT caused a reduction in P-glycoprotein transport at the blood-brain barrier through the lysophosphatidic acid receptor 1. This finding proved significant since it paved the way for the development of new clinical strategies that could increase cerebral penetration of drugs that were associated with pharmacoresistance. The mechanism of action of AMT involves 5 principal routes: norepinephrine transporter block, serotonin transporter block, antagonism of alpha-1 (likely the main receptors related to the management of depression), antagonism of histamine H1 and muscarinic acetylcholine receptors (Fig. 2).

The common adverse effects associated with AMT use are the result of alterations in the normal physiology of the receptors that are affected by the drug. They include acute angle glaucoma, blurred vision, confusion, dizziness, dry mouth, delirium, increased appetite, orthostatic hypotension, sedation, tachycardia, urinary retention and weight gain. Some of the abnormal movements reported in clinical trials of AMT included lack of coordination, ataxia, tremors, restlessness and extrapyramidal symptoms such as tardive dyskinesias (DKN).

In this review, we evaluate the clinical and epidemiological profile, pathological mechanisms and management of AMT-associated movement disorders.

Materials and Methods

The clinical characteristics and definitions of movement disorders such as akathisia (AKT), ballism, chorea, DKN, dystonia (DTN), myoclonus (MCL), Parkinsonism, restless legs syndrome (RLS), tic and tremor were based on the work of Jankovic and Tolosa. Clinical diagnoses of psychiatric conditions were based on the diagnostic criteria published in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, by the American Psychiatric Association. The Naranjo...
algorithm was used to determine the likelihood of whether an adverse drug reaction could be attributed to the drug rather than the result of other factors.16

A search of 6 databases—Excerpta Medica, Google Scholar, Latin American and Caribbean Health Sciences Literature, MEDLINE, Scientific Electronic Library Online and ScienceDirect—was performed to identify case reports, case series, original articles, letters to the editor, bulletins and poster presentations published in electronic form between 1960–2019 on AMT-associated movement disorders. With the aid of Google Translate, the search was expanded to include publications in other languages including Chinese, Dutch, French, German, Italian, Japanese, Korean, Portuguese, Russian and Spanish. The search terms included “akathisia”, “ataxia”, “ballism”, “bradykinesia”, “chorea”, “dyskinesia”, “dystonia”, “hypokinesia”, “hyperkinesia”, “movement disorder”, “myoclonus”, “Parkinsonism”, “restless legs syndrome”, “restlessness”, “stuttering”, “tic” and “tremor”. The terms were also combined with “Amitriptyline, MK-230”.

The authors independently screened the titles and abstracts of all papers that were identified from an initial search. Any disagreements were resolved through discussion between them.

The exclusion criteria included cases where the aetiology of movement disorders was already known and the motor symptoms had not worsened or were not related to AMT. Cases that could not be accessed by electronic means—including lack of response from authors to a formal request by electronic mail—were excluded. Reports of patients who only developed ataxia or tremor after AMT use were not included since details on the neurological examination and clarity in symptom description were lacking. Additionally, both disorders were mainly reported in clinical trials that used questionnaires to assess adverse effects and this could have led to a higher incidence in their reported diagnoses.17 For cases that reported >1 factor that contributed to the development of movement disorders, the Naranjo algorithm was used to evaluate the probability of event occurrence.

Results of the search included details of author, department, year of publication, country of study, number of patients, AMT indication including off-label uses, time from first AMT dose to onset of movement disorder, time from AMT withdrawal to symptom improvement, patient’s status at follow-up and significant findings of clinical history and management. The data were verified twice to ensure proper matching and were organised according to whether the movement disorder was a side effect of AMT use. Finally, categorical variables were presented as counts and continuous variables were shown as mean and standard deviation (SD), and as median and range.

**Results**

A total of 7516 reports were identified from the search, of which 6916 were excluded as they did not meet the inclusion and exclusion criteria (Fig. 3). Most reports did not indicate time of onset of movement disorders and recovery. Between 1960–2019, there were 48 reports of 200 patients—148 in North America, 41 in Europe and 11 in Asia—in 12 countries who developed AMT-associated movement disorders (Table 1).18–65 Figure 4 depicts the trend in the number of AMT-associated movement disorders reported over the same period. AMT-associated movement disorders that were diagnosed in patients included MCL (n = 26), DKN (n = 11), DTN (n = 8), stuttering (n = 5), AKT (n = 3) and restless legs syndrome (n = 1). In less well-defined cases (Table 2), they included DKN (n = 99), psychomotor disturbances (n = 19), Parkinsonism (n = 12), DTN (n = 11), MCL (n = 3), AKT (n = 1) and extrapyramidal symptoms (n = 1).

For well-defined cases, 54 patients were identified and their mean and median ages were 45.40 years (SD 16.78) and 40 years (range 3.7–82 years), respectively. Over half of them were women (58.13%). Indications for AMT included depression (79.54%), insomnia, migraine, neuropathic pain and tension-type headache. Mean and median AMT dose were 126 mg (SD 128.76) and 75 mg (range 15–800 mg), respectively. AMT-associated movement disorders were diagnosed in patients after they were given the drug in the following doses: 15 mg (n = 2), 25 mg (n = 4), 32 mg (n = 1), 50 mg (n = 7), 60 mg (n = 1), 75 mg (n = 9), 100 mg (n = 4), 125 mg (n = 1), 150 mg (n = 11), 200 mg (n = 1), 300 mg (n = 5) and 800 mg (n = 1).

Time of onset of AMT-associated movement disorders was indicated in 44 patients. Mean and median time of onset was 40.95 days (SD 78.08) and 21 days, respectively; in 30 patients, it was <1 month. Duration from AMT withdrawal to complete recovery was described in 37 participants; it was <1 month in 26 patients and >1 month in remaining patients. A weak negative linear correlation (r = -0.0904) was found between start of AMT intake and onset of movement disorders (P = 0.04).

The treatment for AMT-associated movement disorders in 84.44% of patients was withdrawal of AMT. Other interventions included an increase or a reduction in AMT dose and the prescription of medications such as biperiden, diazepam, diphenhydramine, methylphenidate and phenobarbital. Reintroduction of AMT was attempted in 5 patients, but only 1 patient recovered without withdrawal.
7516 reports were identified from a search of 6 databases

600 identified reports were screened

A total of 48 reports on 203 cases were identified

A total of 149 less well-defined cases were found

A total of 54 cases of AMT-associated movement disorders were found

6916 reports were excluded after they failed to meet the inclusion and exclusion criteria

552 reports were excluded due to:
- Complications that were unrelated to AMT use
- Inadequate data
- Lack of electronic access

Fig. 3. Flow chart of search process. AMT: Amitriptyline

Fig. 4. Trend in clinical reports of amitriptyline-associated movement disorders between 1962–2019.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country, Year</th>
<th>Number of Cases</th>
<th>Age (Years)/Gender</th>
<th>Indication</th>
<th>AMT Dose (mg)</th>
<th>AMT Start to MD Onset</th>
<th>AMT Withdrawal to Recovery</th>
<th>Outcome at Follow-Up</th>
<th>Clinical History and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myoclonus</td>
<td></td>
<td></td>
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<tr>
<td>Bockner</td>
<td>UK, 1965</td>
<td>1</td>
<td>37/M</td>
<td>DPS</td>
<td>25</td>
<td>4 days</td>
<td>5 days</td>
<td>CR</td>
<td>CH: maybe cranial and multifocal MCL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CM: AMT withdrawal and perphenazine started with improvement in MCL</td>
</tr>
<tr>
<td>Witton</td>
<td>USA, 1965</td>
<td>1</td>
<td>44/M</td>
<td>DPS</td>
<td>75</td>
<td>7 days</td>
<td>2 days</td>
<td>CR</td>
<td>CH: focal MCL and DTN, normal EEG, possible interaction with thioridazine CM: Methylphenidate and phenobarbital started</td>
</tr>
<tr>
<td>Darcourt et al</td>
<td>France, 1970</td>
<td>3</td>
<td>61/F</td>
<td>DPS</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CR</td>
<td>CH: maybe cranial and multifocal MCL CM: no rechallenge</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CH: multifocal MCL CM: no rechallenge</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>64/F</td>
<td>DPS</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CR</td>
<td>CH: multifocal MCL CM: no rechallenge</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50/F</td>
<td>DPS</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>CR</td>
<td>CH: multifocal MCL and choreiform DKN</td>
</tr>
<tr>
<td>Burks et al</td>
<td>USA, 1974</td>
<td>1</td>
<td>36/F</td>
<td>DPS</td>
<td>Overdose</td>
<td>NA</td>
<td>NA</td>
<td>CR</td>
<td>CH: multifocal MCL, apparent dose-related side effect CM: AMT withdrawal with symptom improvement; AMT rechallenge caused DKN; AMT withdrawal with recovery</td>
</tr>
<tr>
<td>Lippman et al</td>
<td>USA, 1977</td>
<td>1</td>
<td>25/F</td>
<td>DPS</td>
<td>150</td>
<td>3 days</td>
<td>1 day</td>
<td>CR</td>
<td>CH: multifocal MCL, apparent dose-related side effect CM: AMT withdrawal</td>
</tr>
<tr>
<td>Lippman et al</td>
<td>USA, 1977</td>
<td>1</td>
<td>58/F</td>
<td>DPS</td>
<td>125</td>
<td>5 days</td>
<td>1 day</td>
<td>CR</td>
<td>CH: multifocal MCL, apparent dose-related side effect CM: AMT withdrawal</td>
</tr>
<tr>
<td>Koller and Musa</td>
<td>USA, 1985</td>
<td>1</td>
<td>14/NR</td>
<td>DPS</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>CH: multifocal MCL</td>
</tr>
</tbody>
</table>

AKT: Akathisia; AMT: Amitriptyline; CH: Clinical history; CM: Clinical management; CR: Complete recovery; DKN: Dyskinesia; DPS: Depression; DTN: Dystonia; EEG: Electroencephalogram; EPS: Extrapyramidal symptoms; F: Female; HIV: Human immunodeficiency virus; M: Male; MCL: Myoclonus; MD: Movement disorder; NA: Not applicable/not available; NR: Not reported; PKN: Parkinsonism; UK: United Kingdom; USA: United States of America

### Table 1. Summary of Studies on AMT-Associated Movement Disorders (Cont’d)

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Garvey and Tollefson**</td>
<td>USA, 1987</td>
<td>9</td>
<td>40 (mean)/NR</td>
<td>DPS</td>
<td>150–300</td>
<td>2 weeks to 1 month</td>
<td>Weeks to months</td>
<td>CR</td>
<td>CH: Cranial MCL (n = 4), multifocal MCL (n = 3), nocturnal MCL (n =2). CM: AMT withdrawal</td>
</tr>
<tr>
<td>Foerstl et al††</td>
<td>Germany, 1989</td>
<td>1</td>
<td>62/F</td>
<td>DPS</td>
<td>150–300</td>
<td>1 year</td>
<td>1 week</td>
<td>CR</td>
<td>CH: multifocal myoclonus, Creutzfeldt-Jakob syndrome. CM: AMT withdrawal</td>
</tr>
<tr>
<td>Nisijima et al‡‡</td>
<td>Japan, 1996</td>
<td>1</td>
<td>59/M</td>
<td>DPS</td>
<td>75</td>
<td>7 days</td>
<td>11 days</td>
<td>CR</td>
<td>CH: multifocal MCL, possible interaction with trazodone and lithium</td>
</tr>
<tr>
<td>Maher et al§§</td>
<td>Canada, 1997</td>
<td>1</td>
<td>40/M</td>
<td>DPS</td>
<td>25</td>
<td>NR</td>
<td>NR</td>
<td>Death</td>
<td>CH: multifocal MCL, possible differential diagnosis with HIV infection</td>
</tr>
<tr>
<td>Perry</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UK, 1999</td>
<td>1</td>
<td>75/M</td>
<td>DPS</td>
<td>100</td>
</tr>
<tr>
<td>Choi et al¶¶</td>
<td>South Korea, 2006</td>
<td>1</td>
<td>64/M</td>
<td>Tension-type headache</td>
<td>15</td>
<td>8 days</td>
<td>1 day</td>
<td>CR</td>
<td>CH: multifocal MCL CM: AMT withdrawal and clonazepam started with symptom resolution</td>
</tr>
<tr>
<td>Kim and Yum##</td>
<td>South Korea, 2009</td>
<td>1</td>
<td>64/M</td>
<td>Tension-type headache</td>
<td>15</td>
<td>8 days</td>
<td>1 day</td>
<td>CR</td>
<td>CH: multifocal MCL CM: AMT withdrawal and clonazepam started with symptom resolution; AMT rechallenge with reappearance of MCL; AMT withdrawal with full recovery</td>
</tr>
<tr>
<td>Sreejayan and Praharaj***</td>
<td>India, 2013</td>
<td>1</td>
<td>30/M</td>
<td>Migraine</td>
<td>50</td>
<td>NR</td>
<td>8 days</td>
<td>CR</td>
<td>CH: cortical MCL, EEG-based, possible interaction with disulfiram CM: disulfiram withdrawal with recovery</td>
</tr>
</tbody>
</table>

AKT: Akathisia; AMT: Amitriptyline; CH: Clinical history; CM: Clinical management; CR: Complete recovery; DKN: Dyskinesia; DPS: Depression; DTN: Dystonia; EEG: Electroencephalogram; EPS: Extrapyramidal symptoms; F: Female; HIV: Human immunodeficiency virus; M: Male; MCL: Myoclonus; MD: Movement disorder; NA: Not applicable/not available; NR: Not reported; PKN: Parkinsonism; UK: United Kingdom; USA: United States of America


##Kim YD, Yum KS. Tricyclic antidepressant-induced myoclonus: case report and literature review. Mov Disord 2009;24:70.

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<th>Outcome at Follow-Up</th>
<th>Clinical History and Management</th>
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</thead>
<tbody>
<tr>
<td>Paoletti et al†††</td>
<td>Italy, 2018</td>
<td>1</td>
<td>78/M</td>
<td>DPS</td>
<td>60</td>
<td>2 months</td>
<td>NR</td>
<td>CR</td>
<td>CH: multifocal subcortical MCL, normal EEG, stimulus sensitive, Creutzfeldt-Jakob syndrome</td>
</tr>
<tr>
<td>Woogen et al§§§</td>
<td>USA, 1981</td>
<td>1</td>
<td>57/F</td>
<td>DPS</td>
<td>75</td>
<td>4 days</td>
<td>NR</td>
<td>No</td>
<td>CH: orofacial DKN and limb choreiform DKN</td>
</tr>
<tr>
<td>Gangat et al</td>
<td></td>
<td></td>
<td>Ireland, 1987</td>
<td>1</td>
<td>69/F</td>
<td>DPS</td>
<td>75</td>
<td>3 weeks</td>
<td>3 days</td>
</tr>
<tr>
<td>Gourzis et al¶¶¶</td>
<td>Greece, 2004</td>
<td>1</td>
<td>65/F</td>
<td>DPS</td>
<td>50</td>
<td>1 month</td>
<td>1 week</td>
<td>CR</td>
<td>CH: orofacial DKN (rabbit syndrome), possible interaction with paroxetine and perphenazine CM: paroxetine discontinued with symptom resolution</td>
</tr>
</tbody>
</table>

**Table 1. Summary of Studies on AMT-Associated Movement Disorders (Cont’d)**

**Table Legends:**
- AKT: Akathisia
- AMT: Amitriptyline
- CH: Clinical history
- CM: Clinical management
- CR: Complete recovery
- DKN: Dyskinesia
- EPS: Extrapyramidal symptoms
- F: Female
- HIV: Human immunodeficiency virus
- M: Male
- MCL: Myoclonus
- MD: Movement disorder
- NA: Not applicable/not available
- NR: Not reported
- PKN: Parkinsonism
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<th>AMT Withdrawal to Recovery</th>
<th>Outcome at Follow-Up</th>
<th>Clinical History and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson and Whitfield**</td>
<td>UK, 2007</td>
<td>1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1 day</td>
<td>CR</td>
<td>CH: choreiform DKN, positive deficiency of CYP2D6 CM: AMT withdrawal</td>
</tr>
<tr>
<td>Callista and Emidio***</td>
<td>Italy, 2014</td>
<td>1</td>
<td>29/F</td>
<td>Migraine</td>
<td>32</td>
<td>&lt;1 month</td>
<td>1 month</td>
<td>CR</td>
<td>CH: orofacial DKN (rabbit syndrome) CM: AMT withdrawal; diazepam and biperiden started with symptom resolution</td>
</tr>
<tr>
<td>Pawar and Woo****</td>
<td>USA, 2010</td>
<td>1</td>
<td>82/F</td>
<td>Insomnia</td>
<td>50</td>
<td>1 year</td>
<td>2 days</td>
<td>CR</td>
<td>CH: orofacial DKN, possible interaction with amiodarone CM: AMT withdrawal; benzotropine and diphenhydramine started</td>
</tr>
<tr>
<td>Philips and Augustine††††</td>
<td>India, 2017</td>
<td>1</td>
<td>58/F</td>
<td>DPS</td>
<td>75</td>
<td>2 months</td>
<td>10 days</td>
<td>CR</td>
<td>CH: choreoathetoid DKN, history of Parkinson’s disease CM: AMT withdrawal; baclofen and amantadine started with improvement in DKN</td>
</tr>
<tr>
<td>Kumar et al§§§§</td>
<td>India, 2019</td>
<td>1</td>
<td>25/F</td>
<td>NR</td>
<td>25</td>
<td>NR</td>
<td>1 day</td>
<td>CR</td>
<td>CH: orofacial and limb DKN, possible interaction with estrogen and progesterone CM: AMT withdrawal and benzodiazepine started with symptom resolution</td>
</tr>
<tr>
<td>Mithun†††††</td>
<td>India, 2019</td>
<td>1</td>
<td>38/F</td>
<td>Insomnia</td>
<td>25</td>
<td>15 days</td>
<td>6 days</td>
<td>CR</td>
<td>CH: limb DKN CM: AMT withdrawal and clonazepam started with symptom resolution</td>
</tr>
<tr>
<td>Stuttering</td>
<td>UK, 1977</td>
<td>1</td>
<td>48/F</td>
<td>DPS</td>
<td>150</td>
<td>4 days</td>
<td>NR</td>
<td>CR</td>
<td>CH: maybe stuttering, rapid with increase in AMT dose CM: AMT withdrawal</td>
</tr>
</tbody>
</table>

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</thead>
<tbody>
<tr>
<td>Schatzberg et al****</td>
<td>USA, 1978</td>
<td>3</td>
<td>49/F</td>
<td>DPS</td>
<td>200</td>
<td>19 days</td>
<td>NR</td>
<td>NR</td>
<td>CH: maybe stuttering (speech blockage) CM: AMT withdrawal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>40/F</td>
<td>DPS</td>
<td>150</td>
<td>28 days</td>
<td>NR</td>
<td>NR</td>
<td>CH: maybe stuttering (speech blockage) CM: diazepam or increase in AMT dose without improvement in symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>56/M</td>
<td>DPS</td>
<td>150</td>
<td>18 days</td>
<td>NR</td>
<td>NR</td>
<td>CH: maybe stuttering (speech blockage) CM: AMT withdrawal</td>
</tr>
<tr>
<td>Sholomskas*****</td>
<td>USA, 1978</td>
<td>1</td>
<td>25/M</td>
<td>DPS</td>
<td>100</td>
<td>7 days</td>
<td>2 days</td>
<td>CR</td>
<td>CH: maybe stuttering (speech blockage), apparent dose-related side effect CM: AMT withdrawal</td>
</tr>
<tr>
<td>Finder et al†††††</td>
<td>USA, 1982</td>
<td>1</td>
<td>30/M</td>
<td>DPS</td>
<td>75</td>
<td>1 day</td>
<td>NA</td>
<td>CR</td>
<td>CH: cervical DTN (retrocollis) CM: diphenhydramine started with symptom resolution; AMT rechallenge caused symptoms; benztropine started with symptom resolution; AMT rechallenge with no new symptoms</td>
</tr>
<tr>
<td>Lee‡‡‡‡‡</td>
<td>USA, 1988</td>
<td>1</td>
<td>30/F</td>
<td>Insomnia</td>
<td>75</td>
<td>1 day</td>
<td>1 day</td>
<td>CR</td>
<td>CH: segmental upper limb DTN CM: AMT withdrawal</td>
</tr>
<tr>
<td>Ornadel et al§§§§§</td>
<td>UK, 1992</td>
<td>1</td>
<td>20/M</td>
<td>DPS</td>
<td>50</td>
<td>3 months</td>
<td>NR</td>
<td>CR</td>
<td>CH: segmental lower limb with axial and oromandibular DTN CM: AMT withdrawal and procyclidine started with symptom resolution</td>
</tr>
<tr>
<td>Suzuki et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Japan, 1997</td>
<td>1</td>
<td>58/M</td>
<td>DPS</td>
<td>150</td>
</tr>
</tbody>
</table>

AKT: Akathisia; AMT: Amitriptyline; CH: Clinical history; CM: Clinical management; CR: Complete recovery; DKN: Dyskinesia; DPS: Depression; DTN: Dystonia; EEG: Electroencephalogram; EPS: Extrapyramidal symptoms; F: Female; HIV: Human immunodeficiency virus; M: Male; MCL: Myoclonus; MD: Movement disorder; NA: Not applicable/not available; NR: Not reported; PKN: Parkinsonism; UK: United Kingdom; USA: United States of America

<table>
<thead>
<tr>
<th>Study</th>
<th>Country, Year</th>
<th>Number of Cases</th>
<th>Age (Years)/Gender</th>
<th>AMT Dose (mg)</th>
<th>AMT Start to MD Onset</th>
<th>AMT Withdrawal to Recovery</th>
<th>Outcome at Follow-up</th>
<th>Clinical History and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le Doze et al.</td>
<td>France, 1999</td>
<td>1</td>
<td>72/F</td>
<td>Neuropathy</td>
<td>75</td>
<td>&gt;6 weeks</td>
<td>NA</td>
<td>CR: blepharospasm and oromandibular DTN, possible interaction with ranitidine CM: Lowered AMT dose and ranitidine withdrawal with symptom resolution</td>
</tr>
<tr>
<td>Cappuccio et al.</td>
<td>Italy, 2013</td>
<td>1</td>
<td>3.7/F</td>
<td>Neuropathic pain</td>
<td>0.4 mg/kg daily</td>
<td>5 days</td>
<td>NR</td>
<td>CR: apparently segmental inferior limb with cervical (retrocollis) and axial DTN, history of metachromatic leukodystrophy CM: AMT withdrawal</td>
</tr>
<tr>
<td>Gedam et al.</td>
<td>India, 2017</td>
<td>1</td>
<td>32/F</td>
<td>DPS</td>
<td>50</td>
<td>2.5 months</td>
<td>1 day</td>
<td>CR: oromandibular dystonia, possible interaction with paroxetine CM: AMT withdrawal and promethazine started with symptom resolution</td>
</tr>
<tr>
<td>Hiremath and Desai</td>
<td>India, 2016</td>
<td>1</td>
<td>28/M</td>
<td>DPS</td>
<td>50–75</td>
<td>6 months</td>
<td>1 day</td>
<td>CR: cervical DTN CM: AMT withdrawal and promethazine started with DTN recovery</td>
</tr>
<tr>
<td>Krishnan et al.</td>
<td>USA, 1984</td>
<td>1</td>
<td>35/F</td>
<td>DPS</td>
<td>50</td>
<td>Single dose</td>
<td>2 days</td>
<td>CR: possible interaction with estrogen and progesterone CM: AMT withdrawal</td>
</tr>
<tr>
<td>Vandel et al.</td>
<td>France, 1997</td>
<td>1</td>
<td>70/F</td>
<td>DPS</td>
<td>100</td>
<td>1 month</td>
<td>NA</td>
<td>CR: Reduction in AMT dose</td>
</tr>
<tr>
<td>Yotsui et al.</td>
<td>Japan, 2000</td>
<td>1</td>
<td>NR</td>
<td>DPS</td>
<td>NR</td>
<td>NA</td>
<td>NA</td>
<td>CH: likely AMT-induced, AKT developed after epidural droperidol use but was already on AMT and amiodipine</td>
</tr>
</tbody>
</table>

AKT: Akathisia; AMT: Amitriptyline; CH: Clinical history; CM: Clinical management; CR: Complete recovery; DKN: Dyskinesia; DPS: Depression; DTN: Dystonia; EEG: Electroencephalogram; EPS: Extrapyramidal symptoms; F: Female; HIV: Human immunodeficiency virus; M: Male; MCL: Myoclonus; MD: Movement disorder; NA: Not applicable/not available; NR: Not reported; PKN: Parkinsonism; UK: United Kingdom; USA: United States of America


Myoclonus was reported after treatment with antidepressants in Sweden.

Clinical History and Management

Year 35

Number of Cases 1
Country Ireland
Indication Dystonia
Clinical History and Management Report on side effects of AMT use in 1976. The single case was likely a result of the interaction between AMT and perphenazine.

Schimdt et al. Germany 1984 19 Psychomotor disturbances Report on adverse reactions of psychotropic drugs in a psychiatry university hospital; 19 patients reported a psychomotor disturbance after AMT use.

Miller and Jankovic USA 1990 35 Movement disorder Of 125 patients referred for drug-induced movement disorders, 38 had used AMT and perphenazine; 14 had dyskinesia, 9 had dystonia, 11 had Parkinsonism and 1 had akathisia.

Spigset et al. Sweden 1997 3 Myoclonus Myoclonus was reported after treatment with antidepressants in 3 patients who were given daily dose of AMT 50 mg, 75 mg and 100 mg. Some patients had the CYP2D6 inhibitor that could have predisposed them to develop myoclonus.

Madhusoodanan et al. USA 2010 1 Extrapyramidal symptoms A single case of AMT-associated extrapyramidal symptom was lodged with the FDA Adverse Event Reporting System.


Hunter et al. USA 2019 85 Dyskinesia Of 434 patients referred for drug-induced movement disorders, 85 had used AMT and perphenazine.

AMT: Amitriptyline; FDA: Food and Drug Administration; USA: United States of America


After treatment, 47 (95.91%) patients recovered fully, 1 succumbed to human immunodeficiency virus-related complications and 1 experienced a partial recovery.

Discussion

The findings of this review can be summarised with the aid of a hypothetical case based on the information shown in Table 1. After a middle-aged woman of North American origin presented to her psychiatrist with depressive symptoms, she was prescribed AMT 25 mg and the dose was gradually increased to between 100–150 mg. Within 1 month, she returned to the clinic with complaint of involuntary jerks that involved mainly her upper limbs. Results of her laboratory tests were normal and electrodiagnostic studies were not performed. AMT was discontinued without any symptomatic treatment. At follow-up 1 month later, she made a full recovery.

In light of the findings of this review, some of the AMT-associated movement disorders are discussed in the following sections. The pathophysiological mechanisms that are hypothesised to be responsible for the development of movement disorders after the use of AMT are shown in Figure 5.

Myoclonus

MCL was the first movement disorder to be reported after AMT was approved for use in patients by the FDA. MCL patients tended to be men who were prescribed a lower dose of AMT. MCL onset and recovery times were reported to take place within days. Most studies did not report the results of electrodiagnostic examinations in this...
group of patients; in those that did, an abnormal/normal electroencephalogram was reported. Consequently, AMT-induced MCL may have a cortical and subcortical source. MCL can be classified into multifocal, palatal and cranial types. Based on the clinical features suggested by Gupta and Lang, it is possible that cranial MCL is associated with bupropion. It is likely that MCL onset is dose-dependent. A reduction in frequency of bodily jerks was reported after the dose of AMT was lowered in 2 studies, but this result was not replicated in other studies. Additionally, 2 studies reported onset of Creutzfeldt-Jakob syndrome—characterised by rapid cognitive deterioration, MCL and Parkinsonian features—that resolved after AMT was withdrawn. The most common treatment for MCL was withdrawal of AMT. It is also possible that a short trial of benzodiazepine may reduce the symptoms and accelerate recovery.

Like other antidepressants, AMT is thought to trigger off increased serotonin activity that leads to MCL onset. The study by Lhermitte et al was the first to suggest a link between serotonin and the development of MCL. Subsequently, studies have associated the development of MCL with an increase or decrease in serotonin concentration. In particular, findings from animal studies that involved the use of guinea pigs had found that the interaction between 2 serotonin receptors, 5-HT1A and 5-HT2, could induce MCL.

**Dyskinesia**

In DKN, patients present with dyskinetic orofacial, limb or choreoathetoid movements. In 1 patient, DKN reappeared after AMT was withdrawn due to its onset and after trimipramine was prescribed. Consequently, it is possible that DKN can have a class effect and it is probably prudent to abstain from further treatment with other TCA.

In 2 patients, rabbit syndrome was seen. In this condition, perioral tremors occur at a rate of 4–5 Hz and are attributed to the extrapyramidal effects of antipsychotic drugs. Although it is included as an adverse effect in the discussion of DKN in this review, some authors have contended that it should be treated as a different type of disorder.

DKN onset has been attributed to abnormal adaptation of the striatal network that leads to overactivation of the direct pathway. This could be supported by its long onset time in patients that lasted from weeks to months which was longer than the average time of onset.

The interference of AMT with histamine receptors could have also led to the development of DKN. These receptors are commonly found throughout the central nervous system. However, the largest concentration of these receptors are found in the tuberomammillary nucleus which is connected to the cerebral cortex, neostriatum, hypothalamus, hippocampus and nucleus accumbens. Consequently, in susceptible individuals, AMT could have an effect on receptor H1 that led to the release of oxidative species and resulted in striatal disorganisation.

Another possible explanation for DKN onset is a decrease in cholinergic activity induced by AMT use that led to an imbalance in dopamine. In fact, findings from brain autopsy of patients with Huntington’s disease had shown an increase in the ratio of dopamine to acetylcholine.

**Dystonia**

DTN patients tended to be younger and were prescribed a lower dose of AMT. In descending order of frequency, the symptoms of DTN included oromandibular, axial, segmental limb, cervical and blepharospasm movements. In patients with metachromatic leukodystrophy, AMT use at doses that are lower than the maintenance dose can lead to DTN onset. Treatment of DTN involved withdrawal of AMT and complete recovery was achieved within days, even though most reports did not indicate the duration.

In some studies, patients who were on AMT for a longer duration developed DTN after the dose was increased.
Consequently, it is hypothesised that AMT-induced DTN is more likely to be a threshold effect rather than an adverse, linear dose-dependent effect.

It is difficult to attribute the development of DTN to an anticholinergic mechanism since it is well known that anticholinergic medications such as trihexyphenidyl can, in fact, alleviate it. Instead, most researchers believed that DTN develops as a result of an imbalance in dopamine and acetylcholine. Consequently, involvement of a serotoninergic pathway in the striatum may provide a reasonable explanation (Fig. 6). Findings from animal models had shown that the use of selective serotonin inhibitors could increase serotonin concentrations and lead to inactivation of dorsal raphe nucleus. Since dorsal raphe nucleus is believed to control both direct and indirect pathways, its absence or malfunction will likely lead to a rise in dopamine that, in turn, activate in excess the direct pathway that facilitates movement and, eventually, causes DTN.

**Stuttering**

The word “stuttering” was not used in any of the studies; instead, the term “speech blockage” was used. Since there was a lack of clarity in the clinical description and management of patients in the studies, it was possible that they could have presented with oromandibular DTN or palatal MCL which were associated with stuttering.

As all the cases were reported within a short span of 2 years, this finding could be attributed to problems in the formulation of AMT during this period rather than a common pathophysiological mechanism related to the interactions between receptors.

In the patients, AMT dose ranged from moderate to high (100–200 mg). In 1 patient, the stuttering did not improve even after the dose was increased. In another patient, a dose-dependent effect was observed after a reduction in the dose led to a decrease in speech blockage.

**Akathisia**

In clinical practice, it is common knowledge that an association exists between AKT and AMT. However, it was not found in this review and only 3 studies had cited AKT as a possible diagnosis. This movement disorder was even observed in patients who were given a lower dose of AMT. It was treated with either withdrawal of AMT or a reduction in AMT dose that led to resolution of symptoms.

It is likely that AMT-induced AKT is linked to an increase in noradrenergic activity. Findings from studies of rat models had shown that noradrenaline injections promoted the release of dopamine—mainly in the orbitofrontal cortex—and led to hyperactivation of the dopamine receptor D1 which induces restlessness that resembles AKT symptoms in humans.

**Restless Legs Syndrome**

In 1 patient, RLS could be attributed to the interaction between AMT and an oral contraceptive that produced estrogens and progestins which weakened the effect of TCA and increased TCA plasma concentration. A similar finding by Kumar et al led them to suggest it as a possible cause of DKN. Some of the adverse effects associated with AMT use were related to lowered metabolism of cytochrome P450 2D6 (CYP2D6). It is believed that when an increase in the concentration of AMT and NT—not hydroxynortriptyline—takes place, there is a greater likelihood of side effects developing. This was observed in patients with lower metabolic rate or who were on medications that inhibit CYP2D6.

There was only 1 patient who developed RLS after AMT use. However, since this condition is commonly reported in patients who were on other TCA, the finding of RLS in this patient was treated as a class effect.

In their study of the association between antidepressant use, gender and RLS in >1500 patients, Baughman et al
found that AMT-associated RLS was more common in men (relative risk 2.40, confidence interval 1.45–4.00).

The aetiology of AMT-associated RLS is attributed to an increase in serotonergic activity. It is theorised that inhibition of the serotonin transporter leads to a rise in serotonin concentration that has an effect on the intermediodorsal nucleus. This effect causes the postganglionic adrenal glands to release norepinephrine that result in vascular alterations and provoke a sensation of discomfort in the inferior limbs.

Conclusion

AMT is associated with various movement disorders, particularly DKN, DTN and MCL. Stutters and RLS are some of the less common associations. The pathophysiological mechanism of AMT-induced AKT is likely related to norepinephrine; in RLS, it is attributed to norepinephrine and serotonin; in DTN and MCL, it is ascribed to serotonin; and in DKN, histamine and acetylcholine. AMT is the most commonly prescribed TCA, which explains the large number of adverse effects reported from its use in the literature. A correlation between AMT dose and onset of movement disorders has been suggested. Findings on AMT-induced movement disorders can enrich the understanding of the effects of other TCAs. More studies are needed to understand the pathophysiology of AMT and other TCA in movement disorders.

REFERENCES


79. Reed MC, Nijhout HF, Best J. Computational studies of the role of serotonin in the basal ganglia. Front Integr Neurosci 2013;7:41.


