**Appendix Table D125. Treatment discontinuation due to adverse effects with approved and off label drugs vs. placebo, results from individual randomized controlled clinical trials**

| **Active Drug, Daily Dose****Reference** | **Adverse Effect that Resulted in Treatment Discontinuation** | **Sample Size Risk of Bias**  | **Relative Risk****(95% CI)** | **Absolute Risk Difference****(95% CI)** |
| --- | --- | --- | --- | --- |
| **Approved drugs** |  |  |  |  |
| Topiramate 200mgAdelman, 2008 | Hypesthesia | 715Risk of bias Low | 9.8 (0.6 to 164.8) | **0.02 (0.01 to 0.04)** |
| Topiramate 200mgAdelman, 200840 | Dry mouth | 716Risk of bias Low | 2.0 (0.2 to 16.7) | 0.00 (-0.01 to 0.02) |
| Topiramate 200mgAdelman, 200840 | Mood problems | 715Risk of bias Low | 8.2 (0.5 to 139.9) | **0.02 (0.01 to 0.03)** |
| Topiramate 200mgAdelman, 200840 | Weight decrease | 716Risk of bias Low | 5.1 (0.3 to 90.5) | 0.01 (0.00 to 0.02) |
| Topiramate 200mgAdelman, 200840 | Abdominal pain | 716Risk of bias Low | 2.4 (0.5 to 10.4) | 0.01 (-0.01 to 0.03) |
| Topiramate 200mgAdelman, 200840 | Anorexia | 716Risk of bias Low | 5.5 (0.7 to 41.6) | **0.02 (0.01 to 0.04)** |
| Topiramate 200mgAdelman, 200840 | Diarrhea | 716Risk of bias Low | 3.9 (0.5 to 30.5) | 0.01 (0.00 to 0.03) |
| Topiramate 200mgAdelman, 200840 | Dyspepsia | 716Risk of bias Low | 1.2 (0.0 to 28.9) | 0.00 (-0.01 to 0.01) |
| Topiramate 100mgLainez, 200735 | Nausea | 774Risk of bias Low | 1.8 (0.6 to 5.2) | 0.01 (-0.01 to 0.03) |
| Topiramate 100mgAdelman, 200840 | Pharyngitis | 537Risk of bias Low | 2.0 (0.1 to 40.7) | 0.01 (-0.01 to 0.02) |
| Topiramate 200mgAdelman, 200840 | Sinusitis | 716Risk of bias Low | 1.2 (0.0 to 28.9) | 0.00 (-0.01 to 0.01) |
| Topiramate 200mgFreitag, 200736 | Upper respiratory tract infection | 304Risk of bias Low | 0.0 (0.0 to 0.0) | 0.00 (-0.02 to 0.02) |
| Topiramate 100mgAdelman, 200840 | Injury | 537Risk of bias Low | 1.2 (0.0 to 28.8) | 0.00 (-0.01 to 0.01) |
| Topiramate 200mgAdelman, 200840 | Arthralgia | 716Risk of bias Low | 1.2 (0.0 to 28.9) | 0.00 (-0.01 to 0.01) |
| Topiramate 200mgAdelman, 200840 | Back pain | 716Risk of bias Low | 1.2 (0.0 to 28.9) | 0.00 (-0.01 to 0.01) |
| Topiramate 200mgAdelman, 200840 | Abnormal vision | 716Risk of bias Low | 4.3 (0.2 to 78.1) | 0.01 (0.00 to 0.02) |
| Topiramate 75mgBavrasad, 2010232 | Paresthesia | 70Risk of bias Medium | 3.0 (0.1 to 71.2) | 0.03 (-0.05 to 0.10) |
| Topiramate 75mgBavrasad, 2010232 | Nausea | 70Risk of bias Medium | 0.3 (0.0 to 7.9) | -0.03 (-0.10 to 0.05) |
| Topiramate 200mgDiener, 200443 | Fatigue | 288Risk of bias Low | 1.7 (0.8 to 3.7) | 0.04 (-0.02 to 0.11) |
| Topiramate 200mgDiener, 200443 | Difficulty with memory | 288Risk of bias Low | 3.0 (0.3 to 28.5) | 0.01 (-0.01 to 0.04) |
| Topiramate 200mgDiener, 200443 | Insomnia | 288Risk of bias Low | 2.0 (0.7 to 5.7) | 0.03 (-0.02 to 0.09) |
| Topiramate 200mgDiener, 200443 | Somnolence | 288Risk of bias Low | 0.7 (0.1 to 3.9) | -0.01 (-0.04 to 0.02) |
| Topiramate 100mgDiener, 200443 | Taste perversion | 285Risk of bias Low | 0.0 (0.0 to 0.0) | 0.00 (-0.01 to 0.01) |
| Topiramate 200mgDiener, 200443 | Weight decrease | 288Risk of bias Low | 7.0 (0.4 to 134.3) | 0.02 (-0.01 to 0.05) |
| Topiramate 200mgDiener, 200443 | Nausea | 288Risk of bias Low | 3.2 (1.2 to 8.5) | 0.08 (0.02 to 0.14) |
| Divalproex sodium 1000 mgKlapper, 199747 | Abdominal pain | 87Risk of bias Low | 3.1 (0.1 to 73.3) | 0.02 (-0.04 to 0.09) |
| Divalproex sodium 1500 mgKlapper, 199747 | Alopecia | 88Risk of bias Low | 3.0 (0.1 to 71.7) | 0.02 (-0.04 to 0.08) |
| Divalproex sodium 1500 mgKlapper, 199747 | Back pain | 88Risk of bias Low | 3.0 (0.1 to 71.7) | 0.02 (-0.04 to 0.08) |
| Divalproex sodium 500 mgKlapper, 199747 | Constipation | 89Risk of bias Low | 2.9 (0.1 to 70.2) | 0.02 (-0.04 to 0.08) |
| Divalproex sodium 1500 mgKlapper, 199747 | Emotional liability | 88Risk of bias Low | 3.0 (0.1 to 71.7) | 0.02 (-0.04 to 0.08) |
| Divalproex sodium 1500 mgKlapper, 199747 | Gastrointestinal disorder | 58Risk of bias Low | 0.0 (0.0 to 0.0) | 0.00 (-0.10 to 0.10) |
| Divalproex sodium 1500 mgKlapper, 199747 | Nausea | 88Risk of bias Low | 9.0 (0.5 to 162.3) | 0.09 (0.00 to 0.18) |
| Divalproex sodium 1000 mgKlapper, 199747 | Pharyngitis | 87Risk of bias Low | 3.1 (0.1 to 73.3) | 0.02 (-0.04 to 0.09) |
| Divalproex sodium 500 mgKlapper, 199747 | Pneumonia | 89Risk of bias Low | 2.9 (0.1 to 70.2) | 0.02 (-0.04 to 0.08) |
| Divalproex sodium 1500 mgKlapper, 199747 | Somnolence | 88Risk of bias Low | 3.0 (0.1 to 71.7) | 0.02 (-0.04 to 0.08) |
| Divalproex sodium 1500 mgKlapper, 199747 | Thinking abnormal | 88Risk of bias Low | 3.0 (0.1 to 71.7) | 0.02 (-0.04 to 0.08) |
| Divalproex sodium 1500 mgKlapper, 199747 | Vomiting | 88Risk of bias Low | 3.0 (0.1 to 71.7) | 0.02 (-0.04 to 0.08) |
| Divalproex sodium 1500 mgKlapper, 199747 | Weight increase (gain) | 88Risk of bias Low | 3.0 (0.1 to 71.7) | 0.02 (-0.04 to 0.08) |
| Divalproex sodium 1500 mgKlapper, 199747 | Diarrhea | 88Risk of bias Low | 3.0 (0.1 to 71.7) | 0.02 (-0.04 to 0.08) |
| Sodium valproate 1000mg to 1500 mg per dayJensen, 199449 | Dry mouth | 86Risk of bias Medium | 3.0 (0.1 to 71.7) | 0.02 (-0.04 to 0.09) |
| Sodium valproate 1000mg to 1500 mg per dayJensen, 199449 | Tremor | 86Risk of bias Medium | 3.0 (0.1 to 71.7) | 0.02 (-0.04 to 0.09) |
| Sodium valproate 1000mg to 1500 mg per dayJensen, 199449 | Vertigo | 86Risk of bias Medium | 5.0 (0.2 to 101.2) | 0.05 (-0.03 to 0.12) |
| Sodium valproate 1000mg to 1500 mg per dayJensen, 199449 | Weight increase (gain) | 86Risk of bias Medium | 1.0 (0.1 to 15.5) | 0.00 (-0.06 to 0.06) |
| Sodium valproate 1000mg to 1500 mg per dayJensen, 199449 | Abdominal pain | 86Risk of bias Medium | 0.3 (0.0 to 8.0) | -0.02 (-0.09 to 0.04) |
| Sodium valproate 1000mg to 1500 mg per dayJensen, 199449 | Appetite increase | 86Risk of bias Medium | 0.3 (0.0 to 8.0) | -0.02 (-0.09 to 0.04) |
| Sodium valproate 1000mg to 1500 mg per dayJensen, 199449 | Nausea | 86Risk of bias Medium | 7.0 (0.4 to 131.6) | 0.07 (-0.02 to 0.16) |
| Timolol 10mg twice a dayStellar, 198479 | Any adverse event | 94Risk of bias Medium | 5.0 (0.2 to 101.4) | 0.04 (-0.03 to 0.11) |
| Timolol 10mg twice a dayStellar, 198479 | Chest pain(moderate) on day 28 | 94Risk of bias Medium | 3.0 (0.1 to 71.8) | 0.02 (-0.04 to 0.08) |
| Timolol 10mg twice a dayStellar, 198479 | Epigastric distress(severe) and fecal impaction | 94Risk of bias Medium | 3.0 (0.1 to 71.8) | 0.02 (-0.04 to 0.08) |
| **Propranolol 160 mg/dDiener, 200443** | **Fatigue** | **290Risk of bias Low** | **19.3 (1.1 to 327.9)** | **0.06 (0.02 to 0.10)** |
| Propranolol 160 mg/dDiener, 200443 | Difficulty with memory | 290Risk of bias Low | 3.0 (0.1 to 74.0) | 0.01 (-0.01 to 0.03) |
| Propranolol 160 mg/dDiener, 200443 | Somnolence | 193Risk of bias Low | 2.4 (0.1 to 45.9) | 0.02 (-0.02 to 0.06) |
| Propranolol 160 mg/dDiener, 200443 | Weight decrease | 290Risk of bias Low | 0.0 (0.0 to 0.0) | 0.00 (-0.01 to 0.01) |
| Propranolol 160 mg/dDiener, 200443 | Nausea | 193Risk of bias Low | 1.7 (0.2 to 14.2) | 0.01 (-0.04 to 0.06) |
| Propranolol 160 mgPradalier, 198953 | Psoriasis | 55Risk of bias Low | 0.3 (0.0 to 6.1) | -0.04 (-0.14 to 0.06) |
| **Off label drugs** |  |  |  |  |
| Acetazolamide 500 mgVahedi, 200280 | Discontinued due to adverse event | 53Risk of bias Low | 4.7 (1.1 to 19.6) | 0.27 (0.06 to 0.48) |
| Carbamazepine Rompel, 197086 | Discontinued due to adverse event | 96Risk of bias Medium | 3.0 (0.1 to 71.9) | 0.02 (-0.04 to 0.08) |
| Lamotrigine 25 mg-200 mgSteiner, 199787 | Dizziness | 58Risk of bias Low | 6.5 (0.3 to 151.7) | 0.06 (-0.07 to 0.18) |
| Lamotrigine 26 mg-200 mgSteiner, 199787 | Dyspepsia | 59Risk of bias Low | 0.7 (0.0 to 16.0) | -0.03 (-0.11 to 0.06) |
| Lamotrigine 27 mg-200 mgSteiner, 199787 | Nausea | 58Risk of bias Low | 0.7 (0.0 to 16.9) | -0.03 (-0.12 to 0.07) |
| Lamotrigine 28 mg-200 mgSteiner, 199787 | Leucopenia | 58Risk of bias Low | 0.7 (0.0 to 16.9) | -0.03 (-0.12 to 0.07) |
| **Lamotrigine 29 mg-200 mgSteiner, 199787** | **Rash** | **58Risk of bias Low** | **15.6 (2.1 to 117.3)** | **0.36 (0.13 to 0.59)** |
| Oxcarbazepine up to 1,200 mgSilberstein, 200883 | Discontinued due to adverse event | 170Risk of bias Low | 2.0 (0.6 to 6.4) | 0.05 (-0.03 to 0.12) |
| Femoxetine 200 mg-400mg Kangasniemi, 198377 | Discontinued due to adverse event | 58Risk of bias Medium | 7.0 (0.4 to 129.7) | 0.10 (-0.02 to 0.23) |
| Tonabersat 20 mg-40 mgGoadsby, 2009121 | Discontinued due to adverse event | 124Risk of bias Low | 2.2 (0.2 to 23.7) | 0.02 (-0.04 to 0.07) |
| Tonabersat 20 mg-40 mgGoadsby, 2009121 | Dizziness | 124Risk of bias Low | 1.8 (0.5 to 7.4) | 0.04 (-0.05 to 0.13) |
| Atenolol 100mgJohannsson, 198799 | Discontinued due to adverse event | 144Risk of bias Medium | 0.1 (0.0 to 2.7) | -0.04 (-0.09 to 0.01) |
| Bisoprolol 100mgvan de Ven, 1997101 | Discontinued due to adverse event | 115Risk of bias Medium | 1.7 (0.4 to 7.9) | 0.04 (-0.06 to 0.13) |
| Metoprolol 200mgAndersson, 198397 | Discontinued due to adverse event | 71Risk of bias Medium | 1.1 (0.1 to 16.7) | 0.00 (-0.07 to 0.08) |
| Nadolol 80mg -240mgFreitag, 198498 | Bradycardia | 32Risk of bias Low | 1.1 (0.0 to 24.2) | 0.04 (-0.13 to 0.22) |
| Pindolol 7.5 -15mgSjaastad, 197289 | Discontinued due to adverse event | 56Risk of bias Medium | 7.0 (0.4 to 129.5) | 0.11 (-0.02 to 0.23) |
| Nicardipine 40mgLeandri, 1990126 | Dyspepsia | 60Risk of bias Medium | 0.5 (0.0 to 5.2) | -0.03 (-0.14 to 0.08) |
| Verapamil 240mgMarkley, 1984124 | Constipation | 40Risk of bias Medium | 3.0 (0.1 to 69.5) | 0.05 (-0.08 to 0.18) |
| Dihydroergotamine 10mgBousser, 1988233 | Intolerance(alleged) | 90Risk of bias Medium | 0.1 (0.0 to 2.7) | -0.07 (-0.15 to 0.02) |
| Lisuride 0.075 mg Somerville, 1976158 | Discontinued due to adverse event | 150Risk of bias Medium | 2.4 (0.9 to 6.5) | 0.09 (-0.01 to 0.19) |
| Lisuride 0.075 mg Somerville, 1976158 | Fatigue, weakness | 150Risk of bias Medium | 7.0 (0.4 to 133.2) | 0.04 (-0.01 to 0.09) |
| Lisuride 0.075 mg Somerville, 1976158 | Hallucinations | 150Risk of bias Medium | 3.0 (0.1 to 72.5) | 0.01 (-0.02 to 0.05) |
| Lisuride 0.075 mg Somerville, 1976158 | Numbness of tongue | 150Risk of bias Medium | 0.3 (0.0 to 8.1) | -0.01 (-0.05 to 0.02) |
| Lisuride 0.075 mg Somerville, 1976158 | Somnolence (Drowsiness) | 150Risk of bias Medium | 1.0 (0.1 to 15.7) | 0.00 (-0.04 to 0.04) |
| Lisuride 0.075 mg Somerville, 1976158 | Vertigo | 150Risk of bias Medium | 3.0 (0.1 to 72.5) | 0.01 (-0.02 to 0.05) |
| Lisuride 0.075 mg Somerville, 1976158 | Chest pains | 150Risk of bias Medium | 2.0 (0.2 to 21.6) | 0.01 (-0.03 to 0.06) |
| Lisuride 0.075 mg Somerville, 1976158 | Subcutaneous hemorrhage | 150Risk of bias Medium | 0.5 (0.0 to 5.4) | -0.01 (-0.06 to 0.03) |
| Lisuride 0.075 mg Somerville, 1976158 | Blurred vision | 150Risk of bias Medium | 3.0 (0.1 to 72.5) | 0.01 (-0.02 to 0.05) |
| Lisuride 0.075 mg Somerville, 1976158 | Eye irritation | 150Risk of bias Medium | 3.0 (0.1 to 72.5) | 0.01 (-0.02 to 0.05) |
| Lisuride 0.075 mg Somerville, 1976158 | Nausea | 150Risk of bias Medium | 1.0 (0.1 to 6.9) | 0.00 (-0.05 to 0.05) |
| Lisuride 0.075 mg Somerville, 1976158 | Back pains | 150Risk of bias Medium | 3.0 (0.1 to 72.5) | 0.01 (-0.02 to 0.05) |
| Lisuride 0.075 mg Somerville, 1976158 | Impotence | 150Risk of bias Medium | 3.0 (0.1 to 72.5) | 0.01 (-0.02 to 0.05) |
| Methysergide 1 mg q.d.s.Whewell, 1966154 | Discontinued due to adverse event | 148Risk of bias Medium | 0.5 (0.0 to 5.4) | -0.01 (-0.06 to 0.03) |
| Methysergide 1 mg q.d.s.Whewell, 1966154 | Nausea(excessive) | 148Risk of bias Medium | 3.0 (0.1 to 72.5) | 0.01 (-0.02 to 0.05) |
| Tizanidine 4mgSaper, 2002234 | Adverse event other than death | 136Risk of bias Medium | 2.0 (0.6 to 6.2) | 0.06 (-0.03 to 0.16) |
| Tizanidine 4mgSaper, 2002234 | Headache | 136Risk of bias Medium | 2.7 (0.1 to 64.4) | 0.01 (-0.02 to 0.05) |
| Fenoprofen 600 mg TIDCN-00048653 | Fatigue | 75Risk of bias Medium | 0.9 (0.1 to 14.2) | 0.00 (-0.08 to 0.07) |
| Fenoprofen 600 mg TIDSolomon, 1987198 | Adverse effects: fatigue and/or somnolence | Risk of bias Low | 0.9 (0.1 to 14.2) | 0.00 (-0.08 to 0.07) |
| Fenoprofen 600 mg TIDDiamond, 1987235 | Gastrointestinal symptoms | 75Risk of bias Medium | 2.8 (0.3 to 25.4) | 0.05 (-0.05 to 0.15) |
| Tolfenamic Acid 300mgMikkelsen, 1982202 | Discontinued due to adverse event | 76Risk of bias Medium | 2.0 (0.2 to 21.1) | 0.03 (-0.06 to 0.11) |
| Montelukast 20 mgBrandes, 2004203 | Discontinued due to adverse event | 177Risk of bias Low | 0.9 (0.1 to 6.3) | 0.00 (-0.05 to 0.04) |

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0

CI = confidence interval