**Online supplementary material**

**Table 1: Double-blind randomized controlled trials reporting discontinuation symptoms with SNRI treatment**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | | **N** | | **% M** | **Age** | **Primary Diagnosis** | | | | **Design** | **Treatment** | | | | **Weeks treated** | | | **Assessment methods** | | **Rates of discontinuation symptoms** | **Weeks to onset** | **Duration of symptoms** | **Discontinuationmethod** |
| **Single drug and placebo comparisons** | | | | | | | | | | | | | | | | | | | | | | | |
| Fava et al. 1997(11) | | 20 | 55 | | ≥18 | MDD | | | multicenter double-blind RCT | | | | Venlafaxine ER 75-225mg/d (n=10/9) Placebo (n=10/9) | | 8 | | open-ended question | | | DEAE:  Venlafaxine ER (78%) Placebo (22%) p= .03 | 3 days after study drug discontinuation | NA | Taper |
| Raskin et al. 2008(9) | | 311 | 41 | | 65-90 | recurrent MDD | | | multicenter double-blind RCT | | | | Duloxetine 60 mg/d (n=207)  Placebo (n=104) | | 8 | | Spontaneous reports | | | NS | Within 1 week | NA | Taper |
| Rynn et al. 2008(10) | | 327 | 38,2 | | ≥18 | GAD | | | multicenter double-blind RCT | | | | Duloxetine 60-120mg/d (n=168) Placebo (n=159) | | 10 | | Spontaneous reports | | | NS | within 2 weeks | NA | Taper |
| Schagen van Leeuwen et al. 2008(8) | | 265 | 0 | | >65 | SUI  S-MUI | | | multicenter double-blind RCT | | | | Duloxetine 40-80mg/d (n=134/118) Placebo (n=131/119) | | 12 | | NA | | | DEAE:  Duloxetine (21.2%)   Placebo (9.2%)  p=.012 | within 4 weeks | NA | Taper |
| Liebowitz et al. 2009(12) | | 343 | 34,5 | | ≥18 | PD with/without agoraphobia | | | multicenter double-blind RCT | | | | Venlafaxine ER 75-225mg/d (n=175) Placebo (n=168) | | 10 | | NA | | | Taper/poststudy-EAE:  Venlafaxine ER (43%) Placebo (29%) p= .01 | within 2 weeks | NA | Taper |
| Saxe et al. 2012(13) | | 716 | 4 | | 18-70 | FM | | | double-blind RCT | | | | Milnacipran100mg/d (n=357; of which 178 remained on MLN and 178 switched to P)  Placebo (n=359) | | 12 | | NA | | | NS | within 2 weeks | NA | Abrupt |
| Sambunaris et al. 2014(14) | | 429 | ≈35 | | 18-80 | MDD | | | multicenter double-blind RCT | | | | Levomilnacipran ER 40-120mg/d (n=215/164) Placebo (n=214/171) | | 8 | | NA | | | NS | within 2 weeks | NA | Taper |
| **Single drug at different doses and placebo comparisons** | | | | | | | | | | | | | | | | | | | | | | | |
| Allgulander et al. 2001(19) | | 541 | | 39,5 | 18-86 | GAD | | | multicenter double-blind RCT | | Venlafaxine ER 37.5mg/d (n=140) Venlafaxine ER 75mg/d (n=134) Venlafaxine ER 150mg/d (n=137)  Placebo (n=130) | | | | 24 | | BWSQ | | | NS | 24-72h after the last dose of active treatment | 3-7 days | Abrupt |
| Raskin et al. 2005(17) | | 348 | | 46,6 | ≥18 | DPNP | | | multicenter double-blind RCT | | Duloxetine 60mg/d (n=116)  Duloxetine 120mg/d (n=116) Placebo (n=116) | | | | 12 | | NA | | | NS | within 1 week | NA | Taper |
| Koponen et al. 2007(18) | | 513 | | 32,2 | ≥18 | GAD | | | multicenter double-blind RCT | | Duloxetine 60mg/d (n=168) Duloxetine 120mg/d (n=170) Placebo (n=175) | | | | 9 | | Spontaneous reports | | | 1 or more DEAE:  Duloxetine 60mg/d (31.1%) Duloxetine 120mg/d (29.8%)   Placebo (16.2%)  p≤0.05 | within 2 weeks | NA | Abrupt or taper in both DLX 60 and 120 in a randomized fashion |
| Boyer et al. 2008(16) | | 485 | | 30,3 | ≥18 | MDD | | | multicenter double-blind RCT | | Desvenlafaxine 50mg/d (n=166) Desvenlafaxine 100mg/d (n=158)  Placebo (n=161) | | | | 8 | | DESS | | | meanDESS score:  Desvenlafaxine 50mg/d> P at week 1 p=0.001  Desvenlafaxine 100mg/d > P at week 2 p=0.017 | within 1 week | NA | DSVL 100  (Tapered)  DSVL 50  (no tapered) |
| Liebowitz et al. 2008(15) | | 474 | | 40,6 | ≥18 | MDD | | | multicenter double-blind RCT | | Desvenlafaxine 50mg/d (n=158/113) Desvenlafaxine 100mg/d (n=157/109) Placebo (n=159/118) | | | | 8 | | DESS | | | MeanDESS score:  Desvenlafaxine 50mg/d>P at week 1 p=0.001 | within 1 week | NA | DSVL 100 (Tapered)  DSVL 50 (no tapered) |
| **Multiple drugs and placebo comparisons** | | | | | | | | | | | | | | | | | | | | | | | |
| Goldstein et al. 2002(24) | | 173 | | 37 | 18-65 | | MDD | | multicenter double-blind RCT | | Duloxetine 40-120mg/d (n=70) Fluoxetine 20mg/d (n=33)  Placebo (n=70) | | | | 8 | NA | | | | NS | within 1 week | NA | Abrupt |
| Hartford et al. 2007(22) | | 487 | | 37,4 | ≥18 | | GAD | | multicenter double-blind RCT | | Duloxetine 60-120mg/d (n=162) Venlafaxine XR 75-225mg/d (n=164) Placebo (n=161) | | | | 10 | NA | | | | Venlafaxine > Placebo p=.04 | within 2 weeks | NA | Taper |
| Cutler et al. 2009(25) | | 610 | | NS | 18-65 | | MDD | | multicenter double-blind RCT | | Duloxetine 60mg/d (n=149)  Quetiapine XR 150mg/d (n=152)  Quetiapine XR 300mg/d (n=152)  Placebo (n=157) | | | | 6 | TDSS scale | | | | NS | within 2 weeks | NA | Quetiapine 150 (no tapered)  Quetiapine 300 (Tapered)  DLX (Tapered) |
| Tourian et al. 2009(23) | | 615 | | 35,2 | ≥18 | | MDD | | multicenter double-blind RCT | | Desvenlafaxine 50mg/d (n=148) Desvenlafaxine 100mg/d (n=150) Duloxetine 60 mg/d (n=157) Placebo (n=160) | | | | 8 | DESS | | | | DESS:  Desvenlafaxine 50mg/d>P at week1 (p=.002)  Desvenlafaxine 100mg/d>P at week 2 (p=.018)  Duloxetine>P at week 1 and 2 (p=.016; p=.018) | within 2 weeks | NA | Taper |
| Mahableshwarkar et al. 2015(26) | | 614 | | 26.3 | 18-75 | | MDD | | multicenter double-blind RCT | | Duloxetine 60mg/d (n=152) Vortioxetine 15mg/d (n=147) Vortioxetine 20 mg/d (n=154) Placebo (n=161) | | | | 8 | DESS | | | | NS | within 2 weeks | NA | Vortioxetine 15 and 20 (abrupt)  Duloxetine (tapered) |
| **Multiple drugs comparisons** | | | | | | | | | | | | | | | | | | | | | | | |
| Montgomery et al. 2004(29) | 289 | | 28 | | 18-85 | | MDD | multicenter double-blind RCT | | | | Venlafaxine XR 75-150 mg/d (n=143) Escitalopram 10-20 mg/d (n=146) | | RCT: 8 | | DESS | | | Mean number of DESS:  Venlafaxine >Escitalopram p<.001  Change in DESS score ≥4: Venlafaxine>Escitalopram p<.01 | | within 1 week | NA | VNLX 150 (Taper)  Escitalopram 20 (Taper)  VNLX 75 (Abrupt)  Escitalopram 10 (Abrupt) |
| Sechter et al. 2004(27) | 299 | | 29 | | 18-70 | | MDD | multicenter double-blind RCT | | | | Milnacipran 100 mg/d (n=148/46) Paroxetine 20 mg/d (n=151/44) | | 6 | | Spontaneous reports | | | At least 1 DEAE:  Milnacipran (13%)  Paroxetine (31.8%) P=.032 | | within 1 week | NA | Abrupt |
| Vandel et al. 2004 (28)(completion of Sechter et al. 2004) | 53 | | NS | | 18-70 | | MDD | multicenter double-blind RCT | | | | Milnacipran 100 mg/d (n=20) Paroxetine 20 mg/d (n=33) | | (6)+18 | | Spontaneous reports | | | NS | | within 1 week | NA | Abrupt |
| Sir et al. 2005(30) | 163 | | 30.5 | | ≥18 | | MDD, single depressive episode or recurrent depression | Double-blind randomized parallel group study | | | | Venlafaxine 75-225mg/d (N=84) Sertraline 50-150mg/d (N=79) | | 8 + 2 | | ADDS | | | NS | | within 2 weeks | NA | Taper |
| Wade et al. 2007(31) | 294 | | 27.8 | | 18-65 | | MDD | multicenter double-blind RCT | | | | Duloxetine 60 mg/d (n=151) Escitalopram 20 mg/d (n=143) | | RCT: 24 | | Spontaneous reports  Open questions | | | NS | | within 3 weeks | NA | Taper |

ADDS: AntiDepressant Discontinuation Scale; AE: adverse events;BWSQ: benzodiazepine withdrawal symptoms questionnaire; DEAE: discontinuation emergent adverse events;DESS: Discontinuation Emergent Signs and Symptoms; DLX: duloxetine;DPN: diabetic peripheral neuropathy;DPNP: Diabetic Peripheral Neuropathic Pain; DSVL: desvenlafaxine; EAE: emergent adverse events; FM: fibromyalgia;GAD: Generalized Anxiety Disorder;MDD: Major Depressive Disorder; MLN: milnacipran;NA: not available; NS: not significant; P: placebo; PD: panic disorder; PWC: Physician Withdrawal Checklist;RCT: randomized controlled trial; S-MUI: Stress-mixed urinary incontinence; SUI: Stress Urinary Incontinence; TDSS: treatment discontinuation signs and symptoms; VNLX: venlafaxine

**Table 2:Double-blind randomized controlled trials reporting discontinuation symptoms with SNRI treatment after an open trial**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **N** | | **% M** | **Age** | **PrimaryDiagnosis** | **Design** | **Treatment** | **Weeks treated** | **Assessmentmethods** | **Rates of discontinuationsymptoms** | **Weeks to onset** | **Duration of symptoms** | | **Discontinuationmethod** |
| **Single drug at different doses comparisons** | | | | | | | | | | | | | | |
| Chappell et al. 2009(32) | | Open: 350 RCT: 307 | Open: 4.3 | 18.4-83.8 | FM | MulticenterOpen+double-blind RCT | Open  Duloxetine 60mg/d (n=350)  RCT  Duloxetine 60mg/d (n=104)  Duloxetine 120mg/d (n=203) | Open: 8  RCT: 52 | NA | NS | within 2 weeks | NA | | Taper |
| **Single drug and placebo comparisons** | | | | | | | | | | | | | | |
| Perahia et al. 2009(33) | | Open (acute): 514  Open (continuation): 413  RCT: 288 | Open (acute): 30.2  Open (continuation): 29.5  RCT: 28.5 | ≥18 | recurrent MDD | multicenter Open (acute) + Open (continuation)+ double-blind RCT | Open (acute)  Duloxetine 60-120mg/d  Open (continuation) duloxetine 60-120mg/d  RCT Duloxetine 60-120mg/d (n=146)  Placebo (n=142) | Open (acute): 10  Open (continuation): 24  RCT: 52 | Spontaneous report | NS | within 3 weeks | NA | | Open: Taper  RCT: Taper |
| Rickels et al. 2010(34) | | Open: 594 RCT: 375 | Open: 32 RCT: 32.5 | 18-75 | MDD | multicenterOpen+double-blind RCT | Open  Desvenlafaxine 200 or 400 mg/d  RCT  Desvenlafaxine 200 or 400 mg/d (n=190)  Placebo (n=185) | Open: 12  RCT: 6 months | DESS | DESS  Post Open:  P>Desvenlafaxine 200 and 400 mg/d (week 3)  P<0.05  P>Desvenlafaxine 400 mg/d (after week 3) p<0.05  P=Desvenlafaxine 200 mg/d (after week 3)  Post RCT: Desvenlafaxine 400 mg/d > P p=0.029 | within 3 weeks | NA | | Open: Taper  RCT:Taper |
| Rosenthal et al. 2013(35) | | Open:874  RCT: 548 | Open: 30.4 RCT: 28.65 | ≥18 | MDD | Multicenter  Open+double-blind withdrawal RCT | Open Desvenlafaxine 50mg/d  RCT Desvenlafaxine 50mg/d (n=272)  Placebo (n=276) | Open: 20  RCT:6 months | Monitoring of AE | NS | within 2 weeks | NA | | Open: Taper  RCT: Taper |
| **Different discontinuation methods comparisons** | | | | | | | | | | | | | | |
| Gallagher et al. 2012(36) | | Open: 461 RCT (tapering): 384 | 0 | RCT (tapering)  Mean age 54.2 | Healthy postmenopausal women with VMS | Double-blind RCT titrationphase+Open+double-blind RCT tapering phase | Open  Desvenlafaxine 100mg/d  RCT (tapering)  Placebo (n=102)  Desvenlafaxine 50mg/d for 1w+placebo for 1w (n=87)  Desvenlafaxine 50mg/d for 1w+25mg/d for 1w (n=94)  Desvenlafaxine 50mg/d (n=101) | RCT(titration): 1  Open: 15  RCT (tapering): 2 | DESS | Mean DESS score  Taper week 1: AllDesvenlafaxine taper groups < P  p<0.001  Taper week 2:  Desvenlafaxine 50mg/placebo group > P  P=0.009  Taper week 3: Desvenlafaxine 50/25mg> P p=0.005 | Within few days | NA | RCT (tapering):Taper regimens vs  No taper regimen | |
| Khan et al. 2014(7) | | Open: 480 RCT: 357 | 30,5 | ≥18 | MDD | Multicenter  Open+double-blind RCT discontinuation phase | Open  Desvenlafaxine 50mg/d  RCT  Desvenlafaxine 50mg/d (no discontinuation) (n=72)  Desvenlafaxine 25mg/d for 1w+Placebo for 3w (taper) (n=139)  Placebo (abrupt) (n=146) | Open: 24  RCT: 4 | DESS  DSSI | NS | Within 4 weeks | NA | RCT:  No discontinuation  vs  Taper  vs  Abrupt | |

AE: adverse events; DEAE: discontinuation emergent adverse events; DESS: Discontinuation Emergent Signs and Symptoms; DSSI: Discontinuation Symptoms Severity Index; FM: fibromyalgia; MDD: Major Depressive Disorder; NA: not available; NS: not significant; RCT: randomized controlled trial; SAE: serious adverse events; TEAE: treatment emergent adverse events; TPEAE: taper/post-study emergent adverse events; VMS:vasomotor symptoms

**Table 3: Open trials, prospective and retrospective studies reporting discontinuation symptoms with SNRI treatment**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Cases (n)** | **% males** | **Age** | **PrimaryDiagnosis** | **Design** | **Treatment** | **Weeks treated** | **Assessmentmethods** | **Rates of discontinuationsymptoms** | **Weeks to onset** | | **Duration of symptoms** | **Discontinuationmethod** | |
| **Open trials** | | | | | | | | | | | | | | |
| Dallal and Chouinard 1998(38) | 8 | NA | NA | MDD with anxiety symptoms | Open | Venlafaxine 75-225mg/d | 8 | NA | 75% | 8 to 16h after discontinuation (mean 12h) | | Peak on day 4 after complete discontinuation then gradually disappeared | | Taper |
| Raskin et al. 2003(40) | 1279 | 27,4 | 18-87 | MDD | multicenter open trial | Duloxetine 80-120 mg/d | 52 | Spontaneous | DEAE ≥2%:  Dizziness 8.3%  Anxiety 4.3%  Nausea 4.2%  Headache 3.1%  Insomnia 2.9%  Irritability 2.6% | within 2 weeks | | NA | | Abrupt |
| Cohen et al. 2004(39) | 12 | 0 | 22-42 | PMDD | Open | 2 cycles of intermittent treatment: Venlafaxine 37.5mg (2days)-75mg (12d)-37.5mg (2d) and Venlafaxine 75mg (2d)-112.5mg (12d)-75mg (2d) | 16 dayseachcycle | DESS (after discontinuation of each treatment cycle) | 72.7% | 2 to 5 days | | NA | | NA |
| Raskin et al. 2006(41) | 449 | 52,1 | ≥18 | Bilateral DPNP | multi-center randomized open trial | Duloxetine 60mg/d twice daily (n=334) Duloxetine 120mg/d once daily (n=115) | 27 | NA | Duloxetine 60mg/d twice daily11.6%  Duloxetine 120 mg/d  once daily16.2% | within 1 week | | NA | | Taper |
| Perahia et al. 2008(42) | 962 | 35,85 | ≥18 | MDD | Multi-center randomized open trial | Duloxetine 60-120mg/d (n=485) Duloxetine 60-120mg/d + telephone intervention (n=477) | 12 | Spontaneous | Duloxetine9.1%  Duoxetine + telephone intervention 10.7% | within 3 weeks | | NA | | Taper (optional) |
| Tourian et al. 2011(44) | Open:1395 | Open:35 | Open:≥18 | MDD | Double-blind RCT+  multicenter open extension study | DB RCT  Desvenlafaxine 100-400 mg/d  Venlafaxine ER75-225 mg/d  Placebo  Open  Desvenlafaxine200-400 mg/d (n=1395) | DB RCT: 8  Open: 40 | Spontaneous | Open:  42% | within 3 weeks | | NA | | DB RCT: no taper  Open: taper |
| Ferguson et al. 2012(45) | 104 | 40 | 18-75 | MDD | multi-center open trial | Desvenlafaxine 200-400 mg/d | 48 | Spontaneous | 52% | within 3 weeks | | NA | | Taper |
| Mago et al. 2013(43) | Open: 825 | Open: 35 | Open: 18-80 | MDD | Double-blind treatment+ multi-center open extension study | DB Levomilnacipran 40-120 mg/d  Placebo  Open Levomilnacipran ER 40-120 mg/d | DB: 8  Open: 48 | Spontaneous | Open: 9% | within 4 weeks | | NA | | DB: Taper  Open: Taper |
| **Prospective naturalistic study** | | | | | | | | | | | | | | |
| Tint et al. 2008(46) | 28 | 39,3 | 39 mean | MDD | Open randomized naturalistic prospective study | Fluoxetine (n=7) Paroxetine (n=8)  Citalopram (n=5) Fluvoxamine (n=3) Venlafaxine (n=5) | ≥6 | ModifiedDESS | NS | within 3 weeks | NA | | | Short taper  (3days; n=15)  vs  Long taper(14days; n=13) |
| **Restrospective study** | | | | | | | | | | | | | | |
| Baboolal 2004(47) | 68 (7) | 38.2 (14.3) | (21-56) | (MDD with or without other comorbidities) | Retrospective  review | Venlafaxine XR (75 mg/d, 71.4%; 37.5 mg/d, 28.6%) | (13-114) | Provisional  diagnostic  criteria | NS | 25-48 hours | 2-7 days | | | Abrupt |

AE: adverse events; AD: Antidepressant; DB: double-blind; DEAE: discontinuation-emergent adverse event; DESS: Discontinuation-Emergent Signs and Symptoms; DPNP: diabetic peripheral neuropathic pain; MDD: Major Depressive Disorder; NA: not available; NEAE: newly emergent adverse events;NS: not significant; PMDD: Premenstrual dysphoricdisorder*;* RCT: randomized controlled trial

**Table 4: Clinical cases reporting discontinuation symptoms with SNRI treatment**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **References** | **Gender** | **Age** | **Daily dose** | **PrimaryDiagnosis** | **Treatment lenght** | **Abrupt vs gradualstoppage** | **Time to onset of WS** | **Duration of WS** | **Symtomatology** | **Treatment  for WS** |
| **DULOXETINE** | |  |  |  |  |  |  |  |  |  |
| Qadir and Haider 2006(67) | F | 59 | 90 mg/d | recurrent severe MDD | NA | Abrupt | 2 days | NA | two generalized tonic clonicseizures,nausea, clear liquid vomitus, anxiety, electrical sensation inside the body, restlessness, decreased liquid intake, abdominal pain, and decreased sleep | started on a different antidepressant |
| Pitchot and Ansseau 2008(68) | F | 29 | 60 mg/d | single MDD episode | 1st time: 3 months  2nd time: 3 months | 1st time: abrupt  2nd time: taper | 1st time: 36 hours  2nd time: 2 days | 1st time:  8 hours  2nd time:  3 days | nausea, dizziness and very disturbing brain shock-like sensations | 1st time: re-intake of duloxetine 60 mg  2nd time: introduction of fluoxetine for more than 3 months |
| Hou and Lai 2014(69) | F | NA | 60 mg/d | depressed mood, anhedonia, anergia, binge eating and suicide ideation | 1 year | Abrupt switching to bupropion 150 mg/d | 1 day | 10 months | long-term and intermitted (once to twice a week) severe nausea, unexplained fear and dizziness | re-intake of duloxetine 30 mg/dfor 3 months and duloxetine 15 mg/d for 1 monthonlywhen feelingwithdrawal discomfort |
| **MILNACIPRAN** | | | | | | | | | | |
| Williams et al. 2013(70) | M | 40 | 50 mg bid | fibromyalgia | > 1 year | abrupt | 30 hours | NA | stroke-like symptoms, aphasia, right hemiplegia, left-biased gaze deviation,no movements in the right extremities, and spontaneous pill-rolling type activity in the left hand | re-intake of milnacipran 50 mg bid |
| **VENLAFAXINE** | | | | | | | | | | |
| Benazzi 1996(49) | M | 26 | 150 mg/d | dysthymic disorder with atypical features and social phobia | 4 weeks | abrupt | 1 day | 2 days | Brief and frequent bursts of dizziness, headache, nausea, fatigue, insomnia, sweating and worsening of depression | re-intake of venlafaxine 75 mg/d with gradual tapering a week thereafter |
| Farah and Lauer 1996(50) | F | 32 | 300 mg/d | MDD | 1st time: 8 months  2nd time: 1 month | abrupt | 1st time: 36 hours 2nd time: 48 hours | 1-2 hours after treatment was restarted | diffuse headache, nausea, feeling of abdominal distention, fatigue, tinnitus and sensation that congested sinuses | re-intake of venlafaxine 100 mg/d |
| Giakas and Davis 1997(51) | F | 26 | 75 mg bid | MDD | NA | taper | 2-3 hours | NA | dizziness, headache, burst of heat, nausea, malaise | Fluoxetine 10 mg/d |
| Jacobson and Weiber 1997(52) | M | 42 | 150 mg/d | dysthymia with suicidal ideation and threats | 5 months | Taper followed by citalopram 10 mg/d | 9 days | NA | intense anxiety attack with overwhelming suicidal impulses and one acting-out | NA |
| Boyd 1998(53) | M (n=4) F(n=9) | 25-60 | 37.5-600 mg/d | MDD | 2-12 months (mean 7 months) | NA | NA | 2months (n=1) 5days (n=1) 4days (n=1) 2 weeks (n=1)   1 week (n=1) unknown (n=2) no yet  recovered (n=3) recovered (n= 3) | nightmares, nausea, dizziness, anxiety, spatial disorientation, impaired coordination, headache, hypomania, vertigo, insomnia, drowsiness, postural hypotension, blurred vision, numbness, ataxia,sweating, cramps, vomiting, malaise, emotional lability, arthralgia, diarrhea, somnolence, lethargy, paresthesia, hyperesthesia, and syncope | re-intake of venlafaxine and taper (n=1) chlorpromazine (n=1) unknown (n=11) |
| Johnson et al. 1998(54) | M | 42 | 37.5 mg bid | first episode of MDD | 1th time: 6 months  2nd time: 3 weeks | 1th time: taper  2nd time: taper | 1th time: 36 hours | 2nd time: 3 weeks | 1st time: positional vertigo, which caused significant incapacity, nausea and light headedness.  2nd time: ongoing symptoms of vertigo | re-intake of venlafaxine with tapering |
| Parker and Blennerhassett 1998(55) | F | 24 | 300 mg/d | depression | 1th time: 2 months  Other times: within 1 year | 1th time: taper  other times: occasionally missed singledose | Other  times:  4 hours | NA | 1th time: marked headaches and nausea, and considerably worsening of depression  Other times: severe throbbing bilateral headache and nausea | re-intake of venlafaxine 300 mg/d |
| Raby 1998(56) | F | 29 | 150 mg bid | bipolar I disorder | 10 weeks | Taper | NA | NA | nausea, headaches, diarrhea and anxiety so severe to be forced to remain at home. | re-intake of venlafaxine 75mg/d with the addition of ondansetron 4mg bid or tid, followed by taper of both medications |
| Haddad et al. 2001(48) | F | 37 | 225 mg/d | dysthymia and recurrent unipolar depression | 1st time:2 years  2nd time: 1 week  3rdtime:2 weeks | 1st time:taper followed by reboxetine 4 mg bid  2nd time:taper 3rdtime:abrupt | 1st  time:48 hours 2nd time:48 hours | 1st time:2 days | 1st time: hot and cold feelings, sweating, diarrhea, decreased appetite, irritability, slurred speech, a buzzing noise within the head, unsteadiness and weakness in the legs and visual trails or palinopsia. Inability to walk or take a bath unaided and the slurred speech made it difficult to talk  2nd and 3rdtime: irritability, nausea and palinopsia | 1st time:re-intake of venlafaxine XL 75 mg/d  2nd time:re-intake of venlafaxine XL 37.5 mg/d  3rdtime:fluoxetine 20 mg/d for 1 week and then discontinued |
| Luckhaus and Jacob 2001(57) | F | 72 | 150 mg/d | recurrent MDD | NA | Abrupt followed by maprotiline 75 mg/d | 2 days | 11 days | marked, distressing and ongoing agitation, perspiration, nausea and vomiting, tinnitus, sleeplessness | discontinuation of maprotiline and introduction of sertraline 50 mg/d |
| Reeves et al. 2003(58) | M (n=1)  F (n=1) | 45  36 | 75-150 mg/d (n=1)  225 mg/d (n=1) | Depression and alcohol/cocaine abuse (n=2) | several years (n=1)  4 years (n=1) | taper and introduction of fluoxetine 20 mg/d (n=1)  abrupt  or  taper and introduction of citalopram (n=1) | 1 day (n=1) | 5 days (n=1) | little shock-like sensation (n=1)  shock-like sensation in the head, vision of after-images of objects in the field vision (n=1) | re-intake and taper of venlafaxine and introduction of lorazepam |
| Hsiao and Liu 2004(59) | F | 25 | 37.5 mg/d | PMDD | 2 months | Missed one dose | 14 hours | 4 days | disequilibrium features (dizziness, vertigo, ataxia), gastrointestinal symptoms (nausea, irritation), sensory disturbances (paresthesia, shocklike sensations), sleep and psychological symptoms (anxiety, jitteriness and insomnia). The patient could no work and had to rest in bed. | Spontaneously resolved |
| Khazaal 2007(60) | M | 33 | 150 mg/d | GAD | 10 weeks | abrupt | 2 days | 21 days | manic episode with mood elevation, euphoria, impulsive seductive attitudes and decreased of sleep need, engagement in large-scale projects,irritability and aggressive behavior | lorazepam 10 mg/d and valproate |
| Stone et al. 2007(61) | M | 35 | 150 mg/d | recurrent severe depression | Severalyears | abrupt | 36 hours | 24 hours | progressive worsening of anxiety, fearfulness, nausea, motor agitation, confusion, insomnia, anorexia, mood lability and suicidal ideation with suicide attempt | re-intake of venlafaxine 150 mg/d |
| Hsiao and Liu 2008(62) | F | 41 | 150 mg/d | MDD | 1 year and 8 months | Taper (previous attempts: abrupt) | 36-48 hours | NA | severe headache and dizziness (previous attempts: anxiety, palpitations, restlessness, fine tremors, excessive sweating, increased frequency of bowel movements, nausea, vomiting, headache, diarrhea, easy fatigability, general somatic pain and electric shock-like sensations. Associated with significant socio-occupational dysfunction). | cross-taper switching to fluoxetine;  introduction of duloxetine 30-60 mg/d and taper of venlafaxine, with discontinuation of duloxetine 60 mg/d at the end of the fifth week without problems |
| Kotzalidis et al. 2008(63) | F | 31 | 150 mg/d | depression | 20 days | Occasionally  missed doses | NA | NA | agitation, numbness, pricking sensations, sweating, difficulty concentrating and carrying daily activities, weakness, derealisation, reduced ocular lubrification, irritability, fatigue, paresthesia, dizziness, headache, unstable or rapidly changing mood and yawning | NA |
| Clewes 2012(64) | F | 46 | 150 mg/d | severe MDD | 8 years | taper | 1 day | 2 years (tinnitus) | tinnitus, sleep problems, nausea, diarrhea, nightmares anxiety, vomit, lack of appetite, lack of energy, palpitations | NA |
| Wang and Greenberg 2013(65) | F | 76 | 75 mg/d | narcolepsy with cataplexy | NA | episode of diminished absorption from gastroenteritis | 48 hours | 4 hours | precipitation of status cataplecticus that unlike her usual cataplexy episodes which rapidly resolve, last continuously over the next 4 hours. Shemaintainedconsciousnessbutrecalled vividhallucinations. | re-intake of venlafaxine that was gradually increased to 150 mg/ |
| Cutler 2017(66) | F | 43 | 75 mg/d | Chroniccervicalgia and lumbago | 2 months (+ attempts to taper off venlafaxine over the next 4 months) | Initially abrupt discontinuation; successive tapering | 48h | Until pt restarts med | Nausea, vertigo, irritability, chest pain, diaphoresis | duloxetine |

F: female; GAD: Generalized anxiety disorder; M: male; MDD: Major Depressive Disorder; NA: not available; PMDD: Premenstrual dysphoric disorder

**Fig 1. Flow chart of included studies**

Records identified through database search  
(n=3193)

Duplicate entries removed  
(n=849)

Studies for abstract and title evaluation   
(n=2344)

Citation excluded  
(n=2112)

Full-text articles assessed for eligibility  
(n=232)

Excluded because of lack of information about withdrawal symptoms (n=119); not concerned with SNRI (n=3); reviews (n=6); poster (n=4); abstract (n=1); combined data (n=1); pharmacological combination (n=27); non clinical population (n=2); post-hoc analysis (n=1); no data about comparisons (n=7);  
(total=171)

Studies included in the report  
(n=61)

Case reports (n=23)

Open trials (n=8), prospective naturalistic (n=1) and retrospective (n=1) studies

RCTs (n=22)

Open + RCTs (n=6)

**Search strategy**

*Web of Science search strategy*

|  |
| --- |
| 1. (‘Discontinuation OR withdrawal OR rebound’) 2. (‘duloxetine’ OR ‘desvenlafaxine’ OR ‘venlafaxine’ OR ‘milnacipran’ OR ‘levomilnacipran’) 3. (‘SNRI’ OR ‘second generation antidepressant’ OR ‘serotonin norepinephrine reuptake inhibitor’) 4. #1 AND #2 AND #3 5. Limit 4 to Humans 6. Limit 5 to English |

*The Cochrane Library search strategy*

|  |
| --- |
| 1. discontinuation OR withdrawal OR rebound:ti,ab (Word variations have been searched)  2. duloxetine OR desvenlafaxine OR venlafaxine OR milnacipran OR levomilnacipran:ti,ab  3. SNRI OR second generation antidepressant OR serotonin norepinephrine reuptake inhibitor:ti,ab  4. #1 AND #2 AND #3  5. Limit 4 to Humans  6. Limit 5 to English |

*PubMed search strategy*

|  |
| --- |
| 1. (All fields): discontinuation OR withdrawal OR rebound  2. (All fields): duloxetine OR desvenlafaxine OR venlafaxine OR milnacipran OR levomilnacipran  3. (All fields): SNRI OR second generation antidepressant OR serotonin norepinephrine reuptake inhibitor  4. #1 AND #2 AND #3  5. Limit 4 to Humans  6. Limit 5 to English  7. Limit 6 to Adults (19+) |