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



**Table 1. Randomized controlled trials reporting discontinuation symptoms with SSRI treatment**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Cases****(n)** | **%****Males** | **Primary Diagnoses** | **Design** | **Treatments** | **Weeks****Treated** | **Assessment****Method** | **Rates of discontinuation symptoms** | **Weeks** **to onset** | **Discontinuation method** |
| **Single drug and placebo comparisons**  |
| Oehberg et al. 1995 32 | 120 | 24 | Panic disorder | RCT | CT+PXT (n=60)CT+Pbo (n=60) | 12 | Spontaneous reports | Discontinuation symptoms: PXT (34.5%), Pbo (13.5%)  | Within 2 | Abrupt  |
| Zajecka et al. 1998 17 | 395 | - | MDD | Open + RCT | FLX (n=299)Pbo (n=96) | 12+6 | Open ended questions | Somnolence: FXT (10%), Pbo (0%)Dizziness: FXT (4% at week 4, 1% at week 6), Pbo (7% at week 4, 5% at week 6)  | 2 to 6 | Abrupt |
| Markowitz et al. 2000 33 | 226 | - | MDD | Secondary analysis;Open+RCT | CITPbo | 8 | UKU | Rates of CNS events: Pbo (14.8%), CIT (10.9%)Psychiatric symptoms: Pbo (5.6%), CIT (3.1%) | 2 | Abrupt  |
| Montgomery et al. 2005 36 | 371 | 52.5 | SAD | Open+ RCT | ESC (n=190)Pbo (n=181) | 12+24 | DESS | Rates of DESS score >4: ESC (9%), Pbo (27%)  | 1  |  |
| **Multiple drug comparisons** |
| Rosenbaum et al. 1998 22 | 231 | 22.7 | MDD | RCT + RCT | PXT (n=82)SRT (n=79)FLX (n=81)  | 16 to 96 +1 | DESS | Mean score:PXT (7.8±8.55),SRT (5.7±6.96),FLX (0.2±5.22) | 1 | Abrupt |
| Hindmarch et al. 2000 40 | 87 | 32.1 | MDD |  Open + RCT | FXT(n=22)SRT(n=22)PXT(n=22)CIT (n=21) | ≥18 | DESS  | Score>4:CIT 70%FXT 73.3 %SRT 59.1%PXT 100% | ≤1 | Abrupt  |
| Michelson et al. 2000 37 | 107 | 28.9 | MDD | RCT | FXT (n=37)SRT(n=34)PXT(n=36) | 24 to 156 | Checklist(17-item adverse event scale) | Difference between pbo and continuationPXT (4)SRT (0.8)FXT (-1.1)  | <1 | Abrupt  |
| Judge et al. 2002 38 | 150 | 23.3% | MDD | RCT + RCT | PXT (n=75)FXT (n=75)  | 16 to 96 +<1 | DESS | Mean score:PXT (2.2±5.5),FLX (0.2±2.5) | <1 | Abrupt |
| Lader et al. 2004 43 | 839 | 78.8 | SAD | RCT | ESC 5mg (n=167)ESC 10mg (n=167)ESC 20mg (n=170)PXT (n=169)Pbo (n=166) | 24 | DESS | Score >4:ESC 5mg (15.1), ESC 10mg (n=17.1), ESC 20mg (21.7), PXT (28.4), Pbo (1.9) | 1 | Abrupt |
| Montgomery et al. 2004 39 | 192 | 32.5 | MDD | RCT + RCT | PXT (n=61)PXT-Pbo (n=43)Ago (n=61)Ago-Pbo(n=27) | 12+2 | DESS | Mean score:PXT (7.3±7.1), PXT-Pbo(3.5±4.1), Ago (3.0±4.2), Ago-Pbo (4.4±5.7) | 2 | Abrupt |
| Montgomery et al. 2004 41 | 293 | 28 | MDD | RCT | ESC (n=148)VNX (n=145)  | 8 | DESS | Mean score:ESC (2.4), VNX (5) | 1 | Abrupt |
| Sir et al. 2005 42 | 163 | 31 | MDD | RCT | SRT (n=79)VNX (n=84) | 8 | ADDS | Rates of discontinuation symptoms (moderate to severe): SRT (34.3%), VNX (43.5) | 2 | Taper |
| Baldwin et al. 2006 44 | 681 | 35.8 | GAD | RCT | ESC 5mg (n=134)ESC 10mg (n=136)ESC 20mg (n=133)PXT (n=140)Pbo (n=139) | 12 | DESS | Mean score: PXT >Pbo (p<0.001)  | 2 | Only ESC 20mg was tapered  |
| Baldwin et al. 2006 45 | 323 | 42.5 | MDD | RCT+ RCT to early vs long taper  | PXT (n=158)ESC (n=165) | 31 | DESS | No differences between taper strategies.Long Taper mean score:ESC (3.2±4.8), PXT (5.4±8.3)Early taper mean score:ESC (2.6±4.3), PXT (4.4±6.7) | 2 | Taper: 1 week alternate dose vs lower dose at week 1 and alternate dose at week 2 |
| Tint et al. 2008 46 | 28 | 39.3 | MDD | Open + RCT | SSRIs (n=23)VNX (n=5) | >6 | DESS | Short taper:47%Long taper:46% | NS | 3 vs 14 day taper |

*Abbreviations*: *ADDS*, Antidepressant Discontinuation Scale; *CT*, cognitive therapy; *DESS*, Discontinuation Emergent Signs and Symptoms; *GAD*, generalized anxiety disorder; *MDD*, major depressive disorder; *NS*; not specified; *RCT*, randomized controlled trial; *Spontaneous*, passive and incidental reports of discontinuation symptoms; *UKU*, unwanted side-effect scale.

*Treatments*: *Ago*, agomelatine; *ESC*, escitalopram; *FLX*, fluoxetine; *Pbo*, placebo; *PXT*, paroxetine; *SRT*, sertraline;

**Table 2. Open and retrospective trials reporting discontinuation symptoms with SSRI treatment**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Cases****(n)** | **%****Males** | **Primary Diagnoses** | **Design** | **Treatments** | **Weeks****Treated** | **Assessment****Method** | **Rates of discontinuation symptoms** | **Weeks** **to onset** | **Discontinuation method** |
| Black et al. 1993 3 | 14 | NS | PD | Open | FVX | 32 | Spontaneous | 86% | <1 | NS |
| Mallya et al., 1993 48 | 17 | NS | OCD | Open | FVX | 48 to 60 | HSCL-90 | 28% | 2 to 3 | Taper |
| Bogetto et al. 2002 49 | 97 | 41.2 | Dysthymic Disorder | Open  | PXT (n=52)FXT (n=45) | >8 | DESS | PXT=42.3%FXT=8.9% | <1 | Gradual taper (67%) |
| Fava et al. 2007 50 | 20 | 30.0 | Panic Disorder | Open | PXT (n=9)FLX 100-200mg (n=4)FXT (n=3)CIT (n=3)SRT (n=1) | ≥24 | DESS | 45%  | ≤2 | Taper(FLX-SRT 50mg/wk; PXT-FXT-CIT 10mg/wk) |
|  |  |  |  |  |  |  |  |  |  |  |
| Price et al. 1996 53 | 477 | 20.9 | NS | Retrospective | PXT (n=430)SRT (n=20)FLX (n=9)FXT (n=18) | NA | Search ADROIT database for AD induced AE | Of all of SSRI induced AE, withdrawal reaction were:PXT (5.1%)SRT (0.9%)FLX (0.4%)FXT (0.06) | <1 | NS |
| Coupland et al. 1996 52 | 171 | 50.8 | Anxiety and Mood disorders + various | Retrospective | Clomip (n=13)SXT (n=45)FXT (n=20)FLX (n=43)PXT (n=50) | 8 to 24 | Case record review(1 new symptom) | 21/171 (12%):Clomipr (30.8%)PXT (20.0%)FLX (14.0%)SRT (2,2%) | NS | Abrupt and taper |
| Van Geffen et al. 2005 55 | 66 | 24.0 | NS | Retrospective | FXT (n=7)PXT (n=46)FLX(n=7)CIT (n=6) | ≥ 8 | DESS | 59%[Tapered discontin. 52%Abrupt discontin. 86%] | NS | Taper (n=52;78.8%)Abrupt (n=14;21.2%) |
| Himei and Okamura, 2006 54 | 385 | 54.8 | MDD | Retrospective | PXT | - | Diagnosis of SSRI discontinuation syndrome | 10% | <4 | Abrupt and taper |

*Abbreviations*: *ADROIT*, Adverse Drug Reactions On-Line Information Tracking; *DESS*, Discontinuation Emergent Signs and Symptoms; *HSCL-90*, Hopkins Symptoms Checklist; *MDD*, major depressive disorder; *NS*, not specified; *OCD,* Obsessive-compulsive disorder; *PD,* personality disorder; *RCT*, randomized controlled trial;

*Treatments*: *CIT,* Citalopram; *FLX*, fluoxetine; *FVX*, Fluvoxamine; *Pbo*, placebo; *PXT*, paroxetine.

**Table 3. Clinical cases reporting discontinuation symptoms**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **References** | **Gender** | **Age** | **Daily dose** | **Primary diagnosis** | **Treatment length** | **Abrupt vs. gradual stoppage** | **Time to onset of WS (in days)** | **Duration of WS** | **Symptomatology** | **Treatment****for WS** |
| **CITALOPRAM** |  |  |  |  |  |  |  |  |  |  |
| Benazzi, 1998 74 | M | 30 | 20 mg/d | MDDPD | 1 year | 15-10-5 mg/d for 1 week each | 1 | 1 wk | Anxiety, irritability, dizziness |  |
| Fernando and Schwader, 2000 75 | F | 45 | 40 mg/d | Recurrent Depression | NS | Missed dose | 1 | NS | Acute dizziness, light-headedness |  |
| Adson and Kotlyar, 2003 76 | M | 43 | 20 mg/d | Mild Depression | 1 year | 10 mg/d for 1 m or5 mg/d for 2 wk | 4-5 | 2 m | Genitals hypersensitivity; Premature ejaculation |  |
| **ESCITALOPRAM** |  |  |  |  |  |  |  |  |  |  |
| Feth et al. 2006 77 | F | - | 10 mg/d | Depressive symptoms |  | 5 mg/d for 3 wks | 1 wk | 2 wks | Electrical shocks sensations | ESC(10 mg/d) |
| Prakash and Dhar, 2008 78 | M | 35 | 10-20 mg/d | PD | 5 m8 m | 2 missed doses15 mg/d for 3m10 mg/d for 3 m5 mg/d for 3 m | 3 d1 wk | 5 d4 wks | Electrical shocks sensations | ESC(20 mg/d)none |
| **FLUVOXAMINE** |  |  |  |  |  |  |  |  |  |  |
| Szabadi, 1992 2 | F | 30 | 50 mg/d | OCD | NS | NS | NS | NS | Hypomania features, aggressive feelings | FVX(50 mg/d) |
| Benazzi, 1998 72 | F | 33 | 200 mg/d | MDD | 6 m | 150-100-50 mg/d for 3 d each | NS | - | dizziness, paresthesia, nausea, headache, fatigue, loss of appetite, hypersomnia severe aggressiveness, intense irritability, intense agitation. | Clonazepam |
| Hirose, 2001 73 | M | 37 | 150 mg/d | MDD | 6 wk | Missed doses | NS | - | Restless feelings, lack of concentration | FVX(150 mg/d) |
| **FLUOXETINE** |  |  |  |  |  |  |  |  |  |  |
| Cooper, 1988 56 | NS | NS | NS | NS | NS | NS | 2 | NS | agitation, inability to concentrate, insomnia | FLX |
| Stoukides and Stoukides, 1991 1 | M | 32 | NS | MDD | 6 m | NS | 2 | NS | acute dystonic reaction involving the extensors of the neck, back, and upper extremities, torticollis | 50 mg diphenhydramine |
| Kasantikul, 1995 10 | NS | NS | 20 mg/d | NS | 1 year | Abrupt discontinuation | 2 | NS | Acute reversible delirium | FLX(200 mg/d) |
| Einbinder, 1995 5 | F | NS | 40 mg/d | MDD | 5 m | Abrupt discontinuation | 9-14 | NS | Dizziness, light-headedness, “eye twitch” | MeclizineFLX(20 mg/d) |
| Poryazova et al. 2005 57 | F | 57 | 20 mg/d | Narcolepsy | some years | Abrupt discontinuation | - | - | Rebound cataplexy | FLX(20 mg/d) |
| Blum et al. 2008 58 | F | 53 | 40 mg/d | Multiple Sclerosis | 14 years | Abrupt discontinuation | 7 | After Fluoxetine restart | Delirium, confusion, auditory, vivid and emotional liability | FLX(40 mg/d) |
| **PAROXETINE** |  |  |  |  |  |  |  |  |  |  |
| Barr et al. 1994 4 | FFF | 643050 | NS | OCDOCD MDDOCD MDD | 12 wk | 7 d taper10 d taper10 d taper | 373 | 1 wk5 d1 wk | Vertigo, gastrointestinal symptoms, fatigue, myalgia, light-headedness, gait instability, rhinorrhoea, insomnia | None |
| Keuthen and Ricciardi, 1994 60 | M | 3341243738 | 40 to 60 mg/d | OCD | 1-5 months | Taper Discontinuation(only one Abrupt discontinuation) | 1-10 | 4-14 d | Dizziness, light-headedness, nausea, paraesthesia, headache, blackout feelings” | One PXT(20 mg/d) |
| Pyke, 1995 12 | F | 44 | 10/20 mg/d | GAD | 7 wk | NS | 3 | 11 d – 3 wk | Diarrhea, anorexia, nausea, shaking, chills, incoordination, dizziness | Dimenhydrinate 50 mg/dMeclizine |
| Frost and Lal, 1995 9 | MM | 28 | 20-30 mg/d | OCDAnxiety | 2m3 wk | Abrupt discontinuation | 22 | 1-3 wk3 wk | “electrical shocks”, “electric-like waves”;nausea, insomnia, dizziness | PXTNone |
| Phillips, 1995 11 | F | 40 | 20 mg/d | NS | 5 wk | NS | 3 | 1 wk | nausea, headaches, vomiting, abdominal discomfort, agitation | PXT (20 mg/d) |
| Fava and Grandi, 1995 13 | MFF | 432225 | 20 to 40 mg/d | MDDSDMDD | 3 m2 y4 m | Switched to DesipramineNS | 7107 | 4 wk1 wk10 d | vertigo, gait instability, malaise, muscle aches, hypnagogic visual hallucinations;nausea, emesis, myalgia, psychomotor agitation, middle insomnia;fatigue, agitation, rhinorrhoea, myalgia and middle insomnia | DesipramineDesipramineNone |
| Debattista and Schatzberg, 1995 6 | MF | 2646 | 10 mg/d | MDEBD | 4 mNS | Abrupt discontinuation | 21 | NS | sever fatigue, nausea, dizziness, malaise;Emesis, headaches, tremulousness | PXT(10 mg/d) |
| Debattista and Schatzberg, 1995 7 | F | 374836 | 20 to 40 mg/d | MDDDepressive symptomsOCD | 5 m6 m10 wk | Abrupt discontinuation | 342 | 1 wk after Paroxetine restart | dizziness and sleep disturbances (vivid dreams, nightmare and insomnia | PXT(10 - 40 mg/d) |
| Pacheco et al.1996 15 | F | 26/39 | 20 mg/d | MDD | 12-14 m | 2 pt: 14 d taper3 pt: 29 taper | NS | 7 d | vertigo, light-headedness, gait instability | For 2 patient: lorazepam (1 mg/d) |
| Bloch et al. 1995 8 | MM | 3648 | 50 mg/d | Minor Depression | 6 wk | Abrupt discount.Taper in 12 d | 27 | 2.5 wk12 d | Dizziness, blurred vision, nausea, lethargy, insomnia, irritability, homicidal thoughts | None |
| Landry and Roy, 1997 66 | F | 33 | 50 mg/d | MMD | 9 wk | Switched to Desipramine 25 mg/d | 3 | 10 d | Irritability, dysphoria, restlessness, hyperactivity, insomnia, nausea, chills, stomach cramps, diarrhea, mild dizziness | Desipramine 25 mg/d |
| Milliken and Cooper, 1998 61 | FFM | 382645 | 40 mg/d | MDDMDDAnxiety | NSNS2 m | Abrupt discontinuationSwitched to lofepramineAbrupt discontinuation | 2-3 d | 3-10 d | Restlessness, headache, nausea, paraesthesia, “jerkiness”, palpitation, irritability, anxiety, poor concentration, insomnia | PXT(40 mg/d)PXT(40 mg/d)None |
| Shoenberger, 2002 67 | M | NS | 20 mg/d | Depressive symptoms | 3 y | Reduce to 10 mg/d for a wk | 1 | 2-4 wks | Irritability, headache, light-headedness, dizziness, nausea, restless, sleep disturbance | None |
| Mazzatenta et al. 2004 65 | FF | 4050 | 20 mg/d | Depressive symptomsAnxiety and depressive Symptoms | 1 y2 y | Abrupt discontinuation | 1 w15 d | 2 wks | Pruritus | PXT(20 mg/d) |
| Polimeni, et al., 2008 64 | F | 47 | 20 mg/d | SAD | 6 m | 10 mg/d for 15 d10 mg/d alternate | - | - | Nocturnal enuresis | PXT(20 mg/d) |
| Bhanji et al. 2006 59 | F | 73 | 20 mg/d | GADPD | 7 y | Abrupt discontinuation | 30 | 2 wk after Parox restart | waves of anxiety, tension, shortness of breath, palpitations, nausea, feelings of depersonalization, derealisation, initial and middle insomnia | Clonazepam 2-20 mg/dPXT(20 mg/d) |
| Yasui-Furukoriand Kaneko, 2011 63 | FF | 4242 | 20 mg/d20–40 mg/d | MDD | 2 yAbout 2 y | Abrupt10 mg/d for 5 m | 2 d3 d | 1 wk | daytime visual and auditory hallucinations, dizziness, headache, insomnia, nausea | None |
| Belaise et al. 2014 62 | MMW  | 453243 | 20 mg/d to 60mg | MDDPanic with agoraphobiaAnxious depression + panic with agoraphobia | 12 y4 y4 y  | AbruptTapered Tapered  | NS | 2 m5m>3m | Aggressiveness, impulsiveness, electric sensations, visual problems, sleep difficulties, GAD, depersonalization, mood swing  | FVX+CBTClonazepam+CBTCBT |
| **SERTRALINE** |  |  |  |  |  |  |  |  |  |  |
| Louie et al. 1994 68 | F | 46 | 100 mg/d | NS | NS | Abrupt discontinuation | 2 | 14 wk | Fatigue, gastrointestinal distress, sleep disturbance, shortness of breath, impairment of short-term memory and flu-like symptoms | SRT (25 mg/d) |
| Frost and Lal, 1995 9 | M | 22 | 150 mg/d | Dep. | 5 m | 8-week period taper (50 md every 10-20 d) | 1 | 13 wk | “electric shocks” sensations radiating from the neck and chest and down to fingers and toes, brief losses of motor control | None |
| Leiter et al. 1995 14 | FM | 3722 | 100 mg/d | Recurrent MDMDD | 8 m9 m | 75-50 mg/d wkAbrupt | 21 | 1 wk2 wk | Fatigue, irritability, gait instability, slowed thinking, feeling detachment;light-headedness, “whooshing noises” in the ears, vertigo, flu-like symptoms, nausea, diarrhea | None |
| Rosenstock, 1996 16 | MM | 2428 | 100 mg/d | MDD | NS | Taper discontinuation | NS | 3-6 wk | disequilibrium, facial numbness, “pulling sensation to the right” | None |
| Amsdenand Georgian, 1996 71 | M | 29 | 50-100 mg/d | MDE | 6 m | Taper discontinuation | 2 d | 1 wk | Dizziness, Orthostatic hypotension | SRT(50 mg/d) |
| Fava and Grandi, 1995 13 | F | 27 | 50 mg/d | MDD | 6 m | Taper discontinuation | 5 | 1 wk | Severe vertigo gait instability, malaise, headache and muscle aches | None |
| Benazzi, 2002 70 | F | 32 | 50 mg/d | BD II | 2 y | 25 mg/d for one wk | Few days | 2 wk | Anxiety irritability, insomnia, “electrical shocks” | Neuroleptic |
| Levenson, 2009 69 | F | 79 | 200 mg/d | Recurrent Depression | NS | Abrupt discontinuation | 3 | 1 wk | Psychomotor retardation, confusion, muscle rigidity and several extrapyramidal symptoms | Diazepam 15 mg/d; Levodopa 400 mg/d; Benserazide 100 mg/d |

*Abbreviations*: *BD*, Bipolar disorder; *F,* female*; GAD,* generalized anxiety disorder*; M,* male; *MDD*, major depressive disorder; *NS*, not specified; *OCD,* Obsessive-compulsive disorder; *PD,* personality disorder, *SD* Schizoaffective Disorder

*Treatments*: *ESC,* escitalopram*; FLX*, fluoxetine; *FVX*, Fluvoxamine; *PXT*, paroxetine; *SRT*, sertralin