**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 | CIT  Pbo | 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 continuation  PXT (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 | MDD  PD | 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 or  5 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 m  8 m | 2 missed doses  15 mg/d for 3m  10 mg/d for 3 m  5 mg/d for 3 m | 3 d  1 wk | 5 d  4 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” | Meclizine  FLX(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 | F  F  F | 64  30  50 | NS | OCD  OCD MDD  OCD MDD | 12 wk | 7 d taper  10 d taper  10 d taper | 3  7  3 | 1 wk  5 d  1 wk | Vertigo, gastrointestinal symptoms, fatigue, myalgia, light-headedness, gait instability, rhinorrhoea, insomnia | None |
| Keuthen and Ricciardi, 1994 60 | M | 33  41  24  37  38 | 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/d  Meclizine |
| Frost and Lal, 1995 9 | M  M | 28 | 20-30 mg/d | OCD  Anxiety | 2m  3 wk | Abrupt discontinuation | 2  2 | 1-3 wk  3 wk | “electrical shocks”, “electric-like waves”;  nausea, insomnia, dizziness | PXT  None |
| 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 | M  F  F | 43  22  25 | 20 to 40 mg/d | MDD  SD  MDD | 3 m  2 y  4 m | Switched to Desipramine  NS | 7  10  7 | 4 wk  1 wk  10 d | vertigo, gait instability, malaise, muscle aches, hypnagogic visual hallucinations;  nausea, emesis, myalgia, psychomotor agitation, middle insomnia;  fatigue, agitation, rhinorrhoea, myalgia and middle insomnia | Desipramine  Desipramine  None |
| Debattista and Schatzberg, 1995 6 | M  F | 26  46 | 10 mg/d | MDE  BD | 4 m  NS | Abrupt discontinuation | 2  1 | NS | sever fatigue, nausea, dizziness, malaise;  Emesis, headaches, tremulousness | PXT(10 mg/d) |
| Debattista and Schatzberg, 1995 7 | F | 37  48  36 | 20 to 40 mg/d | MDD  Depressive symptoms  OCD | 5 m  6 m  10 wk | Abrupt discontinuation | 3  4  2 | 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 taper  3 pt: 29 taper | NS | 7 d | vertigo, light-headedness, gait instability | For 2 patient: lorazepam (1 mg/d) |
| Bloch et al. 1995 8 | M  M | 36  48 | 50 mg/d | Minor Depression | 6 wk | Abrupt discount.  Taper in 12 d | 2  7 | 2.5 wk  12 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 | F  F  M | 38  26  45 | 40 mg/d | MDD  MDD  Anxiety | NS  NS  2 m | Abrupt discontinuation  Switched to lofepramine  Abrupt 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 | F  F | 40  50 | 20 mg/d | Depressive symptoms  Anxiety and depressive Symptoms | 1 y  2 y | Abrupt discontinuation | 1 w  15 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 d  10 mg/d alternate | - | - | Nocturnal enuresis | PXT(20 mg/d) |
| Bhanji et al. 2006 59 | F | 73 | 20 mg/d | GAD  PD | 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/d  PXT(20 mg/d) |
| Yasui-Furukoriand Kaneko, 2011 63 | F  F | 42  42 | 20 mg/d  20–40 mg/d | MDD | 2 y  About 2 y | Abrupt  10 mg/d for 5 m | 2 d  3 d | 1 wk | daytime visual and auditory hallucinations, dizziness, headache, insomnia, nausea | None |
| Belaise et al. 2014 62 | M  M  W | 45  32  43 | 20 mg/d to 60mg | MDD  Panic with agoraphobia  Anxious depression + panic with agoraphobia | 12 y  4 y  4 y | Abrupt  Tapered  Tapered | NS | 2 m  5m  >3m | Aggressiveness, impulsiveness, electric sensations, visual problems, sleep difficulties, GAD, depersonalization, mood swing | FVX+CBT  Clonazepam+CBT  CBT |
| **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 | F  M | 37  22 | 100 mg/d | Recurrent MD  MDD | 8 m  9 m | 75-50 mg/d wk  Abrupt | 2  1 | 1 wk  2 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 | M  M | 24  28 | 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