**Table 1. Studies reporting excessive arousal-activation with antidepressant treatment of pediatric mood disorders**

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Cases**  **(n)** | **%**  **Males** | **Ages** | **Primary Diagnoses** | **Design** | **Treatments** | **Weeks**  **Treated** | **Assessment**  **Method** | **Behavioral Outcomes** | **Weeks**  **to onset** |
| Tierney et al. 1995 (34) | 33 | 42.2 | 8–18  13.3±2.1 | MDD (psychotic) | Retro | SRT | 6 | Chart review | Activation, hypomania, mania: 18.2% | 2 |
| McConville et al. 1996 (35) | 13 | 23.1 | 12–18  15.1 | MDD±ADHD,  ODD, PTSD | Open | SRT | 12 | Checklist | Insomnia 69%, restless 31%, mania 7.7% | 1 |
| Emslie et al. 1997 (36) | 96 | 79.2 | 7–17  12.4±2.7 | Depression±  anxiety, ADHD, ODD | RCT | FLX (n=48)  Pbo (n=48) | 8 | ––– | Mania+discontinuation: FLX (6.3%), Pbo (0.0%) | 4–7 |
| Alderman et al. 1998 (37) | 61 | 54.1 | 6–17  11.5 | MDD, OCD | Open | SRT | 6 | Spontaneous | Insomnia (34%), behavioral AEs (20%) | ––– |
| Keller et al. 2001 (38) | 275 | 37.8 | 12–18  14.9±1.6 | MDD±anxiety, CDs | RCT | PRX (n=93)  IMI (n=95)  Pbo (n=87) | 8 | ––– | Lability: ADs (4.8%), Pbo (1.1%)  Hostility ADs (5.3%), Pbo (0.0%)  Insomnia: ADs (14.9%), Pbo (3.4%) | ––– |
| Emslie et al. 2002 (39) | 219 | 50.7 | 8–13  12.7±2.6 | MDD±ADHD, ODD | RCT | FLX (n=109)  Pbo (n=110) | 9 | Spontaneous | Mania: FLX (0.9%), Pbo (0.0%) | ––– |
| Bhangoo et al. 2003 (40) | 111 | 64.9 | 6–17  10.9±2.6 | Depression  (probable BPD) | Open | SRIs, Stims, ±APs, MSs | ––– | Open-ended  Inquiry | SRIs: activation (52%), manic symptoms 20%, irritable 9%, insomnia 3% | ––– |
| Carlson & Mick 2003 (41) | 267 | 76.0 | 8.8±2.0 | MDD,ADHD, CD, ODD, anxiety, etc | Retro | SRIs, Stims,  TCAs | ––– | Chart review | SRIs: greatest risk | ––– |
| Wagner et al. 2003 (42) | 376 | 48.9 | 6–17  11.5 | MDD | RCT | SRT (n=189)  Pbo (n=187) | 10 | Spontaneous | Agitation: SRT 7.9%, Pbo (2.1%)  Insomnia: SRT (19.0%), Pbo (8.0%) | ––– |
| Wilens et al. 2003 (43) | 82 | 61.0 | 12.2±3.2 | MDD±anxiety, CDs | Retro | SRIs | ––– | Chart review | Activation: 22%  Irritable/manic: 21%  Insomnia: 17% | ≤12 |
| Faedda et al. 2004 (44) | 82 | 65.8 | 3–17  10.6±3.6 | Depression  (probable BPD) | Retro | SRIs, TCAs,  Stims | ––– | Chart review | Mania: ADs 43.9% | 2 |
| Shirazi & Alaghband-  Rad 2005 (45) | 30 | 46.7 | 8–17  13.5±2.5 | MDD±OCD, phobia, GAD, ODD, ADHD, etc | Open | CTP | 6 | Checklist | Mania-discontinue: 16.7% | 2 |
| Baumer et al. 2006 (46) | 52 | 69.2 | 7–22  15.1±3.4 | Depression  (probable BPD) | Retro | ADs±MSs, APs | ––– | Systematic  Inquiry | Manic symptoms: 50% | 4 |
| Emslie et al. 2006 (47) | 439 | 45.8 | 12–17  14.6±1.5 | MDD | RCT | FLX (n=109),  CBT (n=111),  Both (n=107)  Pbo (n=112) | 12 | Spontaneous | Manic symptoms:  ADs 1.9%, Pbo 0.9% | ––– |
| Gualtieri & Johnson  2006 (48) | 128 | 60.9 | 13.3±2.9 | MDD±ADHD, PDD,  GAD, OCD, ODD | Retro | SRI, SNRI; NDRI | ––– | Test battery | Activation: 28.1% | ––– |
| Zuckerman et al. 2007 (49) | 39 | 66.7 | 5.9±0.8 | Depression±anxiety | Retro | SRIs | 40.4 | Chart review | Activation: 20.5%; 15.4% discontinued | 3 |
| Brent et al. 2008 (50) | 334 | 29.9 | 16.0 | Depression  (unresponsive) | RCT | SRIs (n=85)  VNX (n=83)  SRI+CBT (n=83)  VNX+CBT (n=83) | 12 | Checklist | Irritable: 4.8%  Hypomania: 0.3%  Insomnia: 5.1% | ≤12 |
| **Totals/Means**  **(n=17)** | **2637** | **54.3**  **±15.7** | **12.5**  **±2.6** | **Depression ± Other** | **6/17**  **RCTs** | **ADs ± Others** | **11.8**  **±9.8** | **Various** | **ADs: 16.8±14.6%**  **Pbo: 0.82±0.86%\*** | **4.8**  **±4.3** |

*Abbreviations*: *ADHD*, attention deficit-hyperactivity disorder; *AEs*, adverse events; *BPD*, bipolar disorder; *CBT*, cognitive behavioral therapy; *CDs*, conduct disorders; *GAD*, generalized anxiety disorder; *MDD*, major depressive disorder; *OCD*, obsessive-compulsive disorder; *ODD*, oppositional defiant disorder; *PDD*, pervasive developmental disorder; *RCT*, randomized controlled trial; *Retro*, retrospective or chart review; *Spontaneous*, passive and incidental reports of adverse events.

*Treatments*: *ADs*, antidepressants; *APs*, antipsychotic drugs; *CTP*, citalopram; *FLX*, fluoxetine; *FVX*, fluvoxamine; *IMI*, imipramine; *MSs*, mood-stabilizers; *NDRIs*, norepinephrine-dopamine reuptake inhibitors; *Pbo*, placebo; *Rxs*, treatments; *SDRIs*, serotonin-dopamine reuptake inhibitors; *SNRIs*, serotonin-norepinephrine reupake inhibitors; *SRIs*, serotonin reuptake inhibitors; *SRT*, sertraline; *Stims*, stimulants; *TCAs*, tricyclic antidepressants; *VNX*, venlafaxine. Times: weeks of treatment and latency to excessive mood elevation. [\*] Mean rates of all apparent excessive mood-elevations (based on the highest level of arousal reported in each study) were 20.5-times higher with antidepressants than placebo (*t*=2.40, *p*=0.027).

**Table 2. Studies reporting excessive arousal-activation during antidepressant treatment of pediatric anxiety disorders**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Cases**  **(n)** | **%**  **Males** | **Ages** | **Primary**  **Diagnoses** | **Design** | **Treatments** | **Weeks**  **Treated** | **Outcome**  **Method** | **Behavioral Outcomes** | **Weeks**  **to onset** |
| Riddle et al. 1991 (51) | 285 | 54.2 | 8–16  11.9±2.6 | OCD | Open | FLX | 30 | Spontaneous | Agitation, insomnia: 50% | ––– |
| Fairbanks et al. 1997 (52) | 320 | 50.0 | 9–18  12.0±1.2 | SAD, GAD,  Soc Phobia | Open | FLX | 9 | Checklist | Insomnia: 50%; irritability: 6.2% | ca. 6 |
| March et al. 1998 (53) | 188 | ––– | 6–17  12.6 | OCD | RCT | SRT (n=92)  Pbo (n=95) | 12 | Spontaneous | Agitation+insomnia: SRT (36.9%), Pbo (12.8%) | ––– |
| Cook et al. 2001 (54) | 488 | 51.8 | 6–18  12.5 | OCD | Open | SRT | 12 | Checklist | Insomnia or agitation: 16.1% | ––– |
| Geller et al. 2001 (55) | 103 | 57.3 | 7–17  11.4±3.9 | OCD | RCT | FLX (n=71)  Pbo (n=32) | 13 | Spontaneous | Insomnia: FLX (12.7%), Pbo (9.4%) | ––– |
| Riddle et al. 2001 (56) | 120 | 53.3 | 8–17  13.0 | OCD | RCT | FVX (n=57)  Pbo (n=63) | 10 | Spontaneous | Insomnia: FVX (29.8%), Pbo (9.5%)  Agitation: FVX (12.3%), Pbo (3.2%)  Hypomania: FVX (1.75%), Pbo (0.0%) | ca. 6**a** |
| Rynn et al. 2001 (57) | 22 | 77.3 | 5–17  11.3±3.7 | GAD | RCT | SRT (n=11)  Pbo (n=11) | 9 | Checklist | Restlessness: SRT (54.6%) vs. Pbo (27.3%) | ––– |
| Thomsen et al. 2001 (58) | 17 | 50.0 | 13–18  13.7±2.6 | OCD | Open | CTP+CBT | 104 | Checklist | Aggression or insomnia: 30.0% | ≤10 |
| Liebowitz et al. 2002 (59) | 43 | 58.1 | 8–17  12.7±2.7 | OCD | RCT | FLX (n=21)  Pbo (n=22) | 8 | Checklist | Irritability: FLX (23.8%), Pbo (13.6%)  Excitement: FLX (28.6%), Pbo (13.6%)  Insomnia: FLX (38.1%), Pbo (22.7%) | ––– |
| Walkup et al. 2002 (60,61) | 128 | 50.8 | 6–17  10.4±3.0 | GAD,  Soc Phobia,  SAD, etc. | RCT | FVX (n=63)  Pbo (n=65) | 8 | Spontaneous | Agitation: FVX (27.0%), Pbo (12.3%)  Insomnia: FVX (19.0%), Pbo (20.0%) | ––– |
| Birmaher et al. 2003 (62) | 74 | 45.9 | 7–17  11.8±2.8 | GAD, SAD,  Soc Phobia | RCT | FLX (n=37)  Pbo (n=37) | 12 | Checklist | Excitement: FLX (18.9%), Pbo (10.8%) | ––– |
| Geller et al. 2003 (63) | 528 | 59.1 | 8–17  12.5 | OCD  ±GAD, SAD, depression | Open+  RCT | PRX-a (n=335)  PRX-b (n=95)  Pbo (n=98) | 16 | ––– | Behavioral AEs: PRX-a (11.9%), PRX-b (8.4%), Pbo (11.2%) | ––– |
| March et al. 2004 (64) | 112 | 50.0 | 7–17  11.7 ±2.7 | OCD | RCT | SRT (n=28),  CBT (n=28),  Both (n=28)  Pbo (n=28) | 12 | Checklist | Behavioral AEs: SRT (12.5%), Pbo (3.6%) | ––– |
| Wagner et al. 2004 (65) | 319 | 50.2 | 8–17  13.1±2.8 | Soc Phobia | RCT | PRX (n=163)  Pbo (n=156) | 16 | Spontaneous | Insomnia or agitation: PRX (14.1%), Pbo (5.8%); Mania: PRX (1.8%), Pbo (0.0%) | ––– |
| Clark et al. 2005 (66) | 52 | 44.2 | 7–17  11.8±2.8 | GAD, SAD,  Soc Phobia | Open | FLX (n=42)  None (n=10) | 52 | Spontaneous | Mania: FLX (2.4%), No-Rx (0.0%) | ––– |
| Isolan et al. 2007 (67) | 45 | 30.0 | 10–17  15.0±1.5 | Soc Phobia | Open | *S*-CTP | 12 | ––– | Insomnia: 20%; nervousness: 5.0% | ––– |
| March et al. 2007 (68) | 285 | 45.0 | 8–17  13.6±2.6 | Soc Phobia | RCT | VNX (n=137)  Pbo (n=148) | 16 | Spontaneous | Behavior AEs: VNX (4.4%), Pbo (0%)  Mania: VNX (0.7%), Pbo (0.0%) | ––– |
| Rynn et al. 2007 (69) | 320 | 57.5 | 6–17  11.4±2.9 | GAD | RCT | VNX (n=157)  Pbo (n=163) | 8 | Spontaneous | Behavioral AEs: VNX (6.1%), Pbo (3.2%) | ––– |
| Mrakotsky et al. 2008 (70) | 18 | 50.0 | 8–17  12.1±2.8 | Soc Phobia | Open | MTZ | 8 | Checklist | Irritability: 44.5% | 2 |
| Walkup et al. 2008 (71) | 488 | 50.4 | 7–17  10.7±2.8 | SAD, GAD,  Soc Phobia | RCT | SRT (n=133)  CBT (n=139)  Both (n=140)  Pbo (N=76) | 12 | Checklist | Hyperarousal: SRT (3.7%), Pbo (0.0%) | ––– |
| Alaghband-Rad & Hakimshooshtary 2009 (72) | 29 | 58.6 | 7–18  13.8±3.1 | OCD | RCT | FLX (n=15)  CTP (n=14) | 6 | Spontaneous | Insomnia or hypomania:  FLX (13.3%), CTP (7.1%) | 3 |
| Coskun & Zoroglu 2009 (73) | 6 | 50.0 | 3–5  4.0±0.7 | OCD | Open | FLX | 10 | Checklist | Behavioral AEs: 83.3% | 3 |
| Reinblatt et al. 2009 (74) | 45 | 53.3 | 10.0±2.5 | GAD, SAD,  Soc Phobia | RCT | FVX (n=22)  Pbo (n=23) | 8 | Checklist + inquiry | Activation: FVX (45.4%), Pbo 4.4%) | 4 |
| Harris et al. 2010 (75) | 17 | ––– | 8–17  12.5 | OCD | Retro | FVX | 28 | Chart review | Disinhibition: 17.6% | ––– |
| Schirman et al. 2010 (76) | 78 | 38.5 | 7–18  13.9±2.8 | GAD±MDD | Open | CTP | 8 | Spontaneous | Agitation: 20.5%, insomnia: 15.4%  (10.3% discontinued) | ––– |
| **Totals/Means**  **(n=25)** | **4130** | **51.8**  **±8.6** | **12.0**  **±2.0** | **Anxiety Dxs** | **16/25**  **RCTs** | **SRIs/SNRIs** | **17.6**  **±20.5** | **Various** | **ADs: 22.6±20.3%**  **Pbo: 7.23±7.45%b** | **5.0**  **±3.0** |

*Abbreviations*: *ADHD*, attention deficit-hyperactivity disorder; *AEs*, adverse events; *BPD*, *CBT*, cognitive behavioral therapy; *CDs*, conduct disorders; *GAD*, generalized anxiety disorder; *MDD*, major depressive disorder; *OCD*, obsessive-compulsive disorder; *ODD*, oppositional defiant disorder; *PDD*, pervasive developmental disorder; *RCT*, randomized controlled trial; *Retro*, retrospective or chart review; *SAD*, separation anxiety disorder; *Soc Phobia*, social phobia; *Spontaneous*, passive and incidental reports of adverse events.

*Treatments*: *ADs*, antidepressants; *APs*, antipsychotic drugs; *CTP*, citalopram; *FLX*, fluoxetine; *FVX*, fluvoxamine; *IMI*, imipramine; *MSs*, mood-stabilizers; *NDRIs*, norepinephrine-dopamine reuptake inhibitors; *Pbo*, placebo; *Rxs*, treatments; *SDRIs*, serotonin-dopamine reuptake inhibitors; *SNRIs*, serotonin-norepinephrine reupake inhibitors; *SRIs*, serotonin reuptake inhibitors; *SRT*, sertraline; *Stims*, stimulants; *TCAs*, tricyclic antidepressants; *VNX*, venlafaxine. Times are weeks of treatment and latency to excessive mood-elevation (**a**. for hypomania).

**b**. Observed mean rates of all apparent excessive mood-elevations (based on the highest level of arousal reported in each study) are 2.89-fold higher with antidepressants (ADs) than placebo (*t*=2.89, *p*=0.006).