

## Data supplement

Paper	Type of paper	Level of evidence										Comments	n		
		Symptoms	Medications	Disorders	Incidence	Timing	Management	Response	Akathisia	Suicide	Genetics				
Murphy <i>et al</i> <sup>17</sup>	RCT												5	Describes mechanisms of drug intolerance but does not directly address JAS	246
Oehrborg <i>et al</i> <sup>30</sup>	RCT	4	4	4	4									JAS not primary outcome of trial. No systematic assessment of JAS	120
Pohl <i>et al</i> <sup>33</sup>	RCT	4	4	4	4									JAS not primary outcome of trial. No systematic evaluation of JAS	60
Pohl <i>et al</i> <sup>36</sup>	RCT	4	4	4	4	4								JAS not primary outcome	168
Yeragani <i>et al</i> <sup>12</sup>	RCT	4	2B	4	3B	3B	4							JAS primary outcome. Small numbers per group	52
Zajacka <i>et al</i> <sup>38</sup>	RCT	4	4	4	3B	4								JAS not primary outcome for original trials. Unable to compare early and late side-effects as groups differ	299
Zitrin <i>et al</i> <sup>23</sup>	RCT	4	4	4	4	4	4	4	4	4	5			No systematic rating of side-effects. No between-group comparisons of JAS	111
Ackerman <i>et al</i> <sup>28</sup>	RCT data analysis	4	4	4	4	4					4			Retrospective data analysis from 2 RCTs. JAS not primary outcome of original trials. Drop-out data not included	520
Beasley <i>et al</i> <sup>14</sup>	RCT data analysis	4	4	4	4	4								Post hoc analysis of side-effect data from 3 RCTs. JAS not primary outcome of original trials.	746
Beasley <i>et al</i> <sup>13</sup>	RCT data analysis	4	4	4	4	4								Post hoc analysis of side-effect data from RCT. JAS not primary outcome of original trials	706
Hammad <sup>43</sup>	RCT data analysis	4										4		Analysis of RCT data. Primary outcome of original trials not JAS	4555
Stahl <i>et al</i> <sup>35</sup>	RCT data analysis	4	4	4	3B									Data analysis of 9 RCTs. Finding JAS not primary outcome	–
Tollefson & Saylor <sup>34</sup>	RCT data analysis	4	4	4	2B	4								31 RCTs. Used item 9 of HRDS as proxy measure of agitation	4737
Tollefson <i>et al</i> <sup>42</sup>	RCT data analysis	5	4	4								4		Analysis of 17 RCTs data. Primary outcome of trials not JAS	3065
Akiskal <i>et al</i> <sup>59</sup>	Cohort												5	Opinion in discussion, conceptualising JAS as mixed affective state affecting suicide rate	254
Perlis <i>et al</i> <sup>46</sup>	Cohort												4	Unclear if side-effects elicited relate to JAS	36
Putzhammer <i>et al</i> <sup>45</sup>	Cohort												4	Confounded by use of benzodiazepines on those with early side-effects. Unclear if actigraphy is true measure of JAS	62
Noyes <i>et al</i> <sup>25</sup>	Cohort	5	4	4	4	4	4	4	4	5				Case-note and telephone follow-up. Not masked, no control, subject to reporting and recall bias	107
Harada <sup>15</sup>	Retrospective cohort	4	4	4	4	4					4			Case-note review of uncontrolled cohort. Subject to reporting and recording biases	729
Schneier <i>et al</i> <sup>20</sup>	Retrospective cohort	4	4	4						5				Case-note review of uncontrolled cohort of individuals. JAS not primary outcome	25
Juurink <i>et al</i> <sup>60</sup>	Case-control												5	Comment in discussion regarding JAS and suicide	1138

Table DS1 (continued)

Paper	Type of paper	Level of evidence										Comments	n
		Symptoms	Medications	Disorders	Incidence	Timing	Management	Response	Akathisia	Suicide	Genetics		
Amsterdam <i>et al</i> <sup>10</sup>	Uncontrolled trial	4	4	4	4	4	4	4	4	4	4	No control group. Good monitoring of symptoms	54
Lotufo-Neto <i>et al</i> <sup>27</sup>	Uncontrolled trial	4	4	4	4	4	4	4	4	4	4	Single blind. JAS not primary outcome. No control group	82
Ramos <i>et al</i> <sup>11</sup>	Uncontrolled trial	5	4	4	3B	3B	3B	3B	3B	3B	3B	Non-consecutive sample. Single blind. No comparator treatment	70
Gorman <i>et al</i> <sup>17</sup>	Uncontrolled trial	4	4	4	4	4	4	4	4	4	4	Non-controlled trial. Non-consecutive recruitment. Protocol changed during trial	20
Louie <i>et al</i> <sup>18</sup>	Uncontrolled trial (data analysis)	5	4	4	4	4	4	4	4	4	4	Unmasked, uncontrolled study. Late assessment of side-effects (recall bias)	133
Perlis <i>et al</i> <sup>19</sup>	Uncontrolled trial (data analysis)	4	4	4	4	4	4	4	4	4	4	Based on open uncontrolled trial, JAS not primary outcome. Proxy measures of outcomes	830
Toni <i>et al</i> <sup>2</sup>	Naturalistic open study	4	4	4	2C	2C	2C	2C	2C	2C	2C	No systematic evaluation for JAS. Differential treatment of participants	326
Mark <i>et al</i> <sup>61</sup>	Prescribing database study						5	5	5	5	5	Numerous assumptions regarding prescriptions	
Hu <i>et al</i> <sup>37</sup>	Survey	5	4	4	4	4	4	4	4	4	4	Telephone survey. Participants to recall bias	401
Pohl <i>et al</i> <sup>22</sup>	Case series	4	4	4	4	4	4	4	4	4	4	No masking of assessors. Participants to recording bias. Non-consecutive cases	180
Jackson & Lydiard <sup>24</sup>	Case series	4	4	4	4	4	4	4	4	4	4	Describes 2 cases of JAS	2
Aronson <sup>21</sup>	Case series	4	4	4	4	4	4	4	4	4	4	No structured assessment for JAS. JAS not primary outcome of trial. Non-masked, protocol altered as trial progressed	60
Pohl <i>et al</i> <sup>26</sup>	Case series	4	4	4	4	4	4	4	4	4	4	Description of cases	2
Girischandra <i>et al</i> <sup>62</sup>	Case series											Antidepressant-induced akathisia, no attempt to compare with JAS	2
Liegghio <i>et al</i> <sup>32</sup>	Case series	4	4	4	4	4	4	4	4	4	4	Case reports of buspirone-induced JAS	4
Lipinski <i>et al</i> <sup>40</sup>	Case series											SSRI-induced akathisia compared with JAS	5
Zubenko <i>et al</i> <sup>63</sup>	Case series											Cases of akathisia. No discussion regarding JAS	5
Giesecke <sup>16</sup>	Case study	4	4	4	4	4	4	4	4	4	4	Case describing JAS and its management	1
Eberstein <i>et al</i> <sup>64</sup>	Case											No attempt to distinguish JAS and akathisia	1
Guille <sup>29</sup>	Case	4	4	4	4	4	4	4	4	4	4	1 case, JAS symptoms on dose increase	1
Hansen <sup>65</sup>	Case											SSRI-induced akathisia. No attempt to compare with JAS	1
Olivera <sup>66</sup>	Case											Describes akathisia. No attempt to compare with JAS	1
Vorstman <i>et al</i> <sup>44</sup>	Case	4	4	4	4	4	4	4	4	4	4	Case of JAS-like symptoms with suicidal ideation	1
Yeragani <i>et al</i> <sup>67</sup>	Case	5	5	5	5	5	5	5	5	5	5	Case not described, therefore opinion only	-
NICE <sup>4</sup>	Clinical guideline	5	5	5	5	5	5	5	5	5	5	Clinical guideline	-
Baldwin <i>et al</i> <sup>5</sup>	Clinical guidelines	5	5	5	5	5	5	5	5	5	5	JAS not based upon systematic review	-
FDA <sup>8</sup>	Regulatory body advice	5	5	5	5	5	5	5	5	5	5	Expert opinion	-

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		Symptoms	Medications	Disorders	Incidence	Timing	Management	Response	Akathisia	Suicide	Genetics			
Yeragani <i>et al</i> <sup>54</sup>	Opinion		5						5				Expert opinion. No empirical data	-
Alexander <sup>48</sup>	Review		5	5					5				Expert opinion	-
Argyropoulos <i>et al</i> <sup>51</sup>	Review		5	5					5				Expert opinion	-
Balon <sup>48</sup>	Review									5	5		Expert opinion	-
Culpepper <i>et al</i> <sup>9</sup>	Review	5	5	5						5			Expert opinion	-
Edwards & Anderson <sup>39</sup>	Review	4			4	4							Uses Committee on Safety of Medicine data of medication side-effects	-
Ener <i>et al</i> <sup>55</sup>	Review										5		Expert opinion focused on biological causes of akathisia and JAS	-
Goodman <i>et al</i> <sup>69</sup>	Review	5	5								5		Theoretical discussion regarding JAS driving suicide	-
Lane <sup>53</sup>	Review										5		Review paper regarding pathophysiology of JAS	-
Liebowitz & Klein <sup>50</sup>	Review		5	5					5		5		Expert opinion	-
Lydiard <i>et al</i> <sup>70</sup>	Review		5	5					5				Review	-
Nutt <sup>71</sup>	Review		5						5				Expert opinion	-
Rey & Martin <sup>72</sup>	Review	5	5		5						5		Discussion on JAS and suicidal behaviour in adolescents	-
Sachdev & Kruk <sup>56</sup>	Review										5		No objective data, descriptive review	-
Scott <i>et al</i> <sup>52</sup>	Review		5	5					5				Expert opinion	-
Walkup & Labellarte <sup>73</sup>	Review		5			5			5			5	Expert opinion	-
Westenberg <i>et al</i> <sup>49</sup>	Review		5	5				5					Expert opinion	-
Westenberg <sup>3</sup>	Review		5	5					5				Expert opinion	-
RCT, randomised controlled trial; JAS, jitteriness/anxiety syndrome; NICE, National Institute for Health and Clinical Excellence; FDA, Food and Drug Administration.														

Table DS2 Papers reviewed but not found to contribute to evidence base for the above questions	
Paper	Type of paper/study
Aguglia <i>et al</i> <sup>74</sup>	RCT. JAS not assessed. Differential use of benzodiazepines
Akagi & Kumar <sup>41</sup>	Case series
Bagdy <i>et al</i> <sup>58</sup>	Preclinical data
Bakker <i>et al</i> <sup>75</sup>	Meta-analysis
Baldwin & Birtwistle <sup>76</sup>	Review
Beasley <i>et al</i> <sup>77</sup>	Meta-analysis regarding suicide
Beasley <i>et al</i> <sup>78</sup>	Duplicate data
Beasley <i>et al</i> <sup>79</sup>	Duplicate data
Bennett <i>et al</i> <sup>80</sup>	Review
Blomhoff <i>et al</i> <sup>81</sup>	RCT
Bordet <i>et al</i> <sup>82</sup>	RCT
Burghardt <i>et al</i> <sup>83</sup>	Experiment using rat subjects
Charney & Heninger <sup>84</sup>	Open trial of intravenous tryptophan
Cheung <i>et al</i> <sup>85</sup>	Review
Cowley <i>et al</i> <sup>86</sup>	Case-control study
Damluji & Ferguson <sup>87</sup>	4 cases
De Wilde <i>et al</i> <sup>88</sup>	RCT nil regarding JAS
Den Boer & Westenberg <sup>89</sup>	RCT
Gibbons <i>et al</i> <sup>90</sup>	Cohort study
Gregor <i>et al</i> <sup>91</sup>	Database analysis
Griest <i>et al</i> <sup>92</sup>	Meta-analysis
Gunnell <i>et al</i> <sup>93</sup>	Meta-analysis
Hall & Lucke <sup>94</sup>	Review
Healy & Whitaker <sup>95</sup>	Review
Healy <sup>96</sup>	Review
Khan <i>et al</i> <sup>97</sup>	Review
King <i>et al</i> <sup>98</sup>	Case series
Liebowitz <i>et al</i> <sup>99</sup>	RCT
Musa & Staneluis <sup>100</sup>	Retrospective data analysis of 2 RCTs
Patris <i>et al</i> <sup>101</sup>	RCT, nil regarding JAS
Roy-Byrne <i>et al</i> <sup>102</sup>	Cohort trial follow-up of medications taken by panic disorder participants
Sheehan & Harnett-Sheehan <sup>1</sup>	Review
Simon <i>et al</i> <sup>103</sup>	Cohort
Slaap <i>et al</i> <sup>104</sup>	Open trial
Slaap <i>et al</i> <sup>105</sup>	Pooled data of 2 RCTs
Smith <i>et al</i> <sup>106</sup>	Nil regarding JAS
Stein <i>et al</i> <sup>107</sup>	Review
Tiihonen <i>et al</i> <sup>108</sup>	Cohort study
Toni <i>et al</i> <sup>109</sup>	Duplicate data
Volkers <i>et al</i> <sup>110</sup>	Open trial
Wade <i>et al</i> <sup>111</sup>	RCT

RCT, randomised controlled trial; JAS, jitteriness/anxiety syndrome.

### Additional references

- 59 Akiskal HS, Benazzi F, Perugi G, Rihmer Z. Agitated 'unipolar' depression re-conceptualized as a depressive mixed state: implications for the antidepressant-suicide controversy. *J Affect Disord* 2005; **85**: 245–58.
- 60 Juurlink DN, Mamdani MM, Kopp A, Redelmeier DA. The risk of suicide with selective serotonin reuptake inhibitors in the elderly. *Am J Psychiatry* 2006; **163**: 813–21.
- 61 Mark TL, Kevin M, Torigoe Y. Does the short-term administration of a benzodiazepine improve compliance with antidepressant therapy? ISPOR, 2003 ([http://www.ispor.org/meetings/va0503/posterp\\_s2.asp](http://www.ispor.org/meetings/va0503/posterp_s2.asp)).
- 62 Girishchandra B, Johnson L, Cresp R, Orr K. Mirtazapine induced akathisia. *Med J Aust* 2002; **176**: 242.
- 63 Zubenko G, Cohen B, Lipinski J. Antidepressant-related akathisia. *J Clin Psychopharmacol* 1987; **7**: 254–7.
- 64 Eberstein S, Lenard A, Angrist B. Nefazodone and akathisia. *Biol Psychiatry* 1996; **40**: 798–9.
- 65 Hansen L. Fluoxetine dose-increment related akathisia in depression: Implications for clinical care, recognition and management of selective serotonin reuptake inhibitor-induced akathisia. *J Psychopharmacol* 2003; **17**: 451–2.
- 66 Olivera A. A case of paroxetine-induced akathisia. *Biol Psychiatry* 1996; **39**: 910.
- 67 Yeragani VK, Keshavan M, Pohl R. Tricyclic induced jitteriness – a form of akathisia? *BMJ* 1986; **292**: 1529.
- 68 Alexander PE. Management of panic disorders. *J Psychoactive Drugs* 1991; **23**: 329–33.
- 69 Goodman WK, Murphy TK, Storch EA. Risk of adverse behavioural effects with paediatric use of antidepressants. *Psychopharmacol* 2007; **191**: 87–96.

- 70 Lydiard RB, Brawman-Mintzer O, Ballenger JC. Recent developments in the psychopharmacology of anxiety disorders. *J Consult Clin Psychol* 1996; **64**: 660–8.
- 71 Nutt DJ. Overview of diagnosis and drug treatments of anxiety disorders. *CNS Spectrums* 2005; **10**: 49–56.
- 72 Rey JM, Martin A. Selective serotonin reuptake inhibitors and suicidality in juveniles: review of the evidence and implications for clinical practice. *Child Adolesc Psychiatr Clin N Am* 2006; **15**: 221–37.
- 73 Walkup J, Labellarte M. Complications of SSRI treatment. *J Child Adolesc Psychopharmacol* 2001; **11**: 1–4.
- 74 Aguglia E, Casacchia M, Cassano GB, Faravelli C, Ferrari G, Giordano P, et al. Double-blind study of the efficacy and safety of sertraline versus fluoxetine in major depression. *Int Clin Psychopharmacol* 1993; **8**: 197–202.
- 75 Bakker A, van Balkom AJ, Spinhoven P. SSRIs vs. TCAs in the treatment of panic disorder: a meta-analysis. *Acta Psychiatr Scand* 2002; **106**: 163–7.
- 76 Baldwin DS, Birtwistle J. The side effect burden associated with drug treatment of panic disorder. *J Clin Psychiatry* 1998; **59** (suppl 8): 39–44.
- 77 Beasley Jr CM, Dornseif BE, Bosomworth JC, Saylor ME, Rampey Jr AH, Heiligenstein JH, et al. Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *BMJ* 1991; **303**: 685–92.
- 78 Beasley Jr CM, Nilsson ME, Koke SC, Gonzales JS. Efficacy, adverse events, and treatment discontinuations in fluoxetine clinical studies of major depression: a meta-analysis of the 20-mg/day dose. *J Clin Psychiatry* 2000; **61**: 722–8.
- 79 Beasley Jr CM, Bosomworth JC, Wernicke JF. Fluoxetine: relationships among dose, response, adverse events, and plasma concentrations in the treatment of depression. *Psychopharmacol Bull* 1990; **26**: 18–24.
- 80 Bennett J, Moloff M, Stanton S, Dwight M, Keck P. A risk-benefit assessment of pharmacological treatments for panic disorder. *Drug Safety* 1998; **18**: 419–30.
- 81 Blomhoff S, Haug TT, Hellstrom K, Holme I, Humble M, Madsbu HP, et al. Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. *Br J Psychiatry* 2001; **179**: 23–30.
- 82 Bordet R, Thomas P, Dupuis B. Effect of pindolol on onset of action of paroxetine in the treatment of major depression: intermediate analysis of a double-blind, placebo-controlled trial. *Reseau de Recherche et d'Experimentation Psychopharmacologique. Am J Psychiatry* 1998; **155**: 1346–51.
- 83 Burghardt NS, Sullivan GM, McEwen BS, Gorman JM, LeDoux JE. The selective serotonin reuptake inhibitor citalopram increases fear after acute treatment but reduces fear with chronic treatment: a comparison with tianeptine. *Biol Psychiatry* 2004; **55**: 1171–8.
- 84 Charney D, Heninger M. Serotonin function in panic disorders. *Arch Gen Psychiatry* 1986; **43**: 1059–65.
- 85 Cheung AM, Dewa CS, Levitt A. Clinical review of mania, hostility and suicide-related events in children and adolescents treated with antidepressants. *Paediatric Child Health* 2005; **10**: 457–63.
- 86 Cowley DS, Ha EH, Roy-Byrne PP. Determinants of pharmacologic treatment failure in panic disorder. *J Clin Psychiatry* 1997; **58**: 555–61.
- 87 Damluji NF, Ferguson JM. Paradoxical worsening of depressive symptomatology caused by antidepressants. *J Clin Psychopharmacol* 1988; **8**: 347–9.
- 88 De Wilde J, Spiers R, Mertens C, Bartholome F, Schotte G, Leyman S. A double-blind, comparative, multicentre study comparing paroxetine with fluoxetine in depressed patients. *Acta Psychiatr Scand* 1993; **87**: 141–5.
- 89 Den Boer JA, Westenberg HG. Serotonin function in panic disorder: a double blind placebo controlled study with fluvoxamine and ritanserin. *Psychopharmacology (Berl)* 1990; **102**: 85–94.
- 90 Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Mann JJ. Relationship between antidepressants and suicide attempts: an analysis of the Veterans Health Administration data sets. *Am J Psychiatry* 2007; **164**: 1044–9.
- 91 Gregor KJ, Riley JA, Downing DK. Concomitant use of anxiolytics and hypnotics with selective serotonin reuptake inhibitors. *Clin Ther* 1996; **18**: 521–7.
- 92 Greist JH, Jefferson JW, Kobak KA, Katzelnick DJ, Serlin RC. Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder. A meta-analysis. *Arch Gen Psychiatry* 1995; **52**: 53–60.
- 93 Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRAS safety review. *BMJ* 2005; **330**: 385.
- 94 Hall W, Lucke J. How have the selective serotonin reuptake inhibitor antidepressants affected suicide mortality? *Aust N Z J Psychiatry* 2006; **40**: 941–50.
- 95 Healy D, Whitaker C. Antidepressants and suicide: risk-benefit conundrums. *J Psychiatry Neurosci* 2003; **28**: 331–7.
- 96 Healy D. Lines of evidence on the risks of suicide with selective serotonin reuptake inhibitors. *Psychother Psychosom* 2003; **72**: 71–9.
- 97 Khan A, Khan S, Kolts R, Brown W. Suicide rates in clinical trials of ssris, other antidepressants and placebo: analysis of FDA reports. *Am J Psychiatry* 2003; **160**: 790–2.
- 98 King RA, Riddle MA, Chappell PB, Hardin MT, Anderson GM, Lombroso P, et al. Emergence of self-destructive phenomena in children and adolescents during fluoxetine treatment. *J Am Acad Child Adolesc Psychiatry* 1991; **30**: 179–86.
- 99 Liebowitz MR, Stein MB, Tancer M, Carpenter D, Oakes R, Pitts CD. A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder. *J Clin Psychiatry* 2002; **63**: 66–74.
- 100 Musa M, Staneluis J. Adverse events of fluoxetine: Postmarketing compared with premarketing clinical trials. *J Clin Psychiatry* 2007; **61**: 874.
- 101 Patris M, Bouchard JM, Bougerol T, Charbonnier JF, Chevalier JF, Clerc G, et al. Citalopram versus fluoxetine: a double-blind, controlled, multicentre, phase III trial in patients with unipolar major depression treated in general practice. *Int Clin Psychopharmacol* 1996; **11**: 129–36.
- 102 Roy-Byrne P, Russo J, Dugdale DC, Lessler D, Cowley D, Katon W. Undertreatment of panic disorder in primary care: role of patient and physician characteristics. *J Am Board Fam Pract* 2002; **15**: 443–50.
- 103 Simon GE, Savarino J, Operskalski B, Wang PS. Suicide risk during antidepressant treatment. *Am J Psychiatry* 2006; **163**: 41–7.
- 104 Slaap BR, van Vliet IM, Westenberg H, Den Boer J. MHPG and heart rate as correlates of nonresponse to drug therapy in panic disorder patients. *Psychopharmacology* 1996; **127**: 353–8.
- 105 Slaap BR, van Vliet IM, Westenberg HG, Den Boer JA. Responders and non-responders to drug treatment in social phobia: differences at baseline and prediction of response. *J Affect Disord* 1996; **39**: 13–9.
- 106 Smith WT, Londborg PD, Glaudin V, Painter JR. Short-term augmentation of fluoxetine with clonazepam in the treatment of depression: a double-blind study. *Am J Psychiatry* 1998; **155**: 1339–45.
- 107 Stein RE, Zitner LE, Jensen PS. Interventions for adolescent depression in primary care. *Pediatrics* 2006; **118**: 669–82.
- 108 Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Tanskanen A, Haukka J. Antidepressants and the risk of suicide, attempted suicide and overall mortality in a nationwide cohort. *Arch Gen Psychiatry* 2006; **63**: 1358–67.
- 109 Toni C, Perugi G, Frare F, Mata B, Akiskal HS. Spontaneous treatment discontinuation in panic disorder patients treated with antidepressants. *Acta Psychiatr Scand* 2004; **110**: 130–7.
- 110 Volkens AC, Tulen JH, van den Broek WW, Bruijn JA, Passchier J, Peplinkhuizen L. 24-Hour motor activity after treatment with imipramine or fluvoxamine in major depressive disorder. *Eur Neuropsychopharmacol* 2002; **12**: 273–8.
- 111 Wade AG, Lepola U, Koponen HJ, Pedersen V, Pedersen T. The effect of citalopram in panic disorder. *Br J Psychiatry* 1997; **170**: 549–53.