

Review article

Antidepressant-induced jitteriness/anxiety syndrome: systematic review

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Background

Early worsening of anxiety, agitation and irritability are thought to be common among people commencing antidepressants, especially for anxiety disorders. This phenomenon, which may be termed jitteriness/anxiety syndrome, is cited as an explanation for early treatment failure and caution in using selective serotonin reuptake inhibitors (SSRIs). However, we believe that it is inconsistently defined and that robust evidence to support the phenomenon is lacking.

Aims

To review systematically all evidence relating to jitteriness/anxiety syndrome to identify: constituent symptoms; medications implicated; disorders in which it was reported; incidence; time course; management strategies; relationship of this syndrome to therapeutic response; distinction between syndrome and akathisia; relationship between syndrome and suicide; and genetic predispositions.

Method

A systematic search identified articles and these were included in the review if they addressed one of the above aspects of jitteriness/anxiety syndrome.

Results

Of 245 articles identified, 107 articles were included for review. No validated rating scales for jitteriness/anxiety syndrome were identified. There was no robust evidence that the incidence differed between SSRIs and tricyclic antidepressants, or that there was a higher incidence in anxiety disorders. Published incidence rates varied widely from 4 to 65% of people commencing antidepressant treatment. Common treatment strategies for this syndrome included a slower titration of antidepressant and the addition of benzodiazepines. Conclusive evidence for the efficacy of

these strategies is lacking. There was conflicting and inconclusive evidence as to whether the emergence of this syndrome had a predictive value on the response to treatment. It appears to be a separate syndrome from akathisia, but evidence for this assertion was limited. The effect of jitteriness/anxiety syndrome on suicide rates has not been evaluated. Three studies examined genetic variations and side-effects from treatment, but none was specifically designed to assess jitteriness/anxiety syndrome.

Conclusions

Jitteriness/anxiety syndrome remains poorly characterised. Despite this, clinicians' perception of this syndrome influences prescribing and it is cited to support postulated mechanisms of drug action. We recommend systematised evaluation of side-effects at earlier time points in antidepressant trials to further elucidate this clinically important syndrome.

Declaration of interest

There are no direct conflicts of interest relating to any of the authors and the contents of this work. This study was not commissioned, funded or sponsored by any pharmaceutical company or other financial enterprise. Over the past 20 years D.J.N. and his research group (which during the period in which the review was designed and conducted has included S.J.C.D., S.D.H., D.M.C., S.S. A.R. and L.I.S) have received funds (research grants, speakers fees or consultancy payments) from every major pharmaceutical company with an interest in the psychiatric field. D.J.N. has also received legal fees from companies, medical defence organisations and the British Legal Aid board in relation to court cases regarding the effects of psychotropic drugs. He holds approximately 300 GlaxoSmithKline shares.

Many people starting antidepressants experience transient worsening in anxiety, agitation and irritability. Medical literature^{1–3} and guidelines^{4,5} cite this phenomenon, advising caution when prescribing selective serotonin reuptake inhibitors (SSRIs), especially for anxiety disorders. This phenomena is also used to support theoretical hypotheses of antidepressant action.⁶ However, we believe it remains inconsistently and poorly defined. For consistency in this systematic review we use the term jitteriness/anxiety syndrome to encompass the range of symptoms reported as part of the early antidepressant activation phenomena.

To clarify the evidence base for jitteriness/anxiety syndrome we systematically reviewed all existing evidence relating to it, addressing the following questions: what symptoms constitute jitteriness/anxiety syndrome; which medications are implicated; in which disorders has it been reported; what is the incidence; what is the time course; what management strategies are effective; what is the relationship to therapeutic response; what is the relationship between this syndrome and akathisia; what is the relationship between this syndrome and suicide; is there a genetic predisposition?

Method**Search strategy**

We systematically searched online databases (Medline, PubMed, ProQuest and Cochrane) from January 1966 to May 2006 for all relevant English language articles. We used the following search terms: jitteriness; jitteriness syndrome; activation (syndrome); initiation (syndrome) alone as well as in combination with either SSRI OR serotonin reuptake inhibitor OR tricyclic antidepressant; drug-induced akathisia; SSRI AND early onset OR psychomotor agitation OR aggression OR hostility OR impulsivity; and TCA/tricyclic OR SSRI AND initial AND anxiety. We scrutinised reference lists for other relevant articles.

Study selection and ranking

A total of 245 articles were identified. Abstracts were assessed for inclusion by two independent investigators. We expected to find limited information; therefore, articles were included from all

levels of evidence provided they were judged to address one of the predefined questions. Examination of the abstracts revealed 138 were uninformative, often pertaining to different syndromes (usually neonatal jitteriness). Thus 107 articles were assessed for inclusion. Included papers were independently reviewed by two investigators (D.M.C. and S.J.C.D.) for relevance to each question in turn. The overall evidence for each question was evaluated with the following scheme using the Oxford Centre of Evidence-based Medicine Levels of Evidence⁷: evidence level A consistent grade 1 studies; level B consistent grade 2 or 3 studies (or extrapolations from grade 1 studies); level C grade 4 studies (or extrapolations from grade 2 or 3 studies); level D grade 5 evidence or troubling inconsistencies in evidence.

Our ranking deviated slightly from the Oxford Centre of Evidence-based Medicine Levels of Evidence in the following manner. Anticipating most articles to be ranked at the lower grades, we distinguished case studies and small case series from papers consisting entirely of authors' opinions by ranking single case descriptions and small case series as level 4. Therefore only papers addressing one of our predetermined questions but containing neither objective evidence nor case descriptions were ranked as level 5. If papers were relevant for more than one question they received specific rankings for their utility in answering each question. Differences between investigators on article ranking were resolved by direct discussion. Papers addressing jitteriness/anxiety syndrome, but not pertaining to one of the predetermined questions were looked at separately.

Results

Online Table DS1 contains all 66 articles providing evidence relevant to the questions, with independent rankings for each

question addressed. Online Table DS2 contains the remaining 41 articles found not to be relevant to any of these questions.

What symptoms constitute jitteriness/anxiety syndrome?

Despite being described almost 30 years ago, no studies were designed to validate a cluster of symptoms that may constitute jitteriness/anxiety syndrome. Therefore, descriptions of the syndrome vary and are of evidence level D. Thirteen papers described jitteriness/anxiety syndrome or activating symptoms. Although symptoms such as insomnia, anxiety, irritability, increased energy and restlessness appear in most descriptions (Table 1) consistency is lacking and no symptom is ubiquitous. The Food and Drug Administration (FDA) advisory⁸ and subsequent commentary by Culpepper *et al*⁹ suggest hypomania and mania are symptoms of the 'activation syndrome'. However, this approach, based on expert opinion not experimental evidence, constitutes a departure from previous literature.

Amsterdam *et al*,¹⁰ Ramos *et al*¹¹ and Yeragani *et al*¹² devised scales based on subjective reports to quantify symptom severity. None of these scales have been validated or used in subsequent research, nor were objective measures incorporated. Therefore, we are currently unable to determine a reliable framework for description or quantification of symptoms.

Which medications are implicated?

Evidence from randomised placebo-controlled double-blind trials suggests both imipramine and fluoxetine cause jitteriness/anxiety syndrome. Yeragani *et al*¹² performed a randomised controlled trial (RCT) of early side-effects in treating panic disorder and related this to serum iron levels. Imipramine was significantly

Table 1 Contrasting descriptions of constituent symptoms of jitteriness/anxiety syndrome

Zitrin <i>et al</i> ²³	Gorman <i>et al</i> ¹⁷	Pohl <i>et al</i> ²²	Yeragani <i>et al</i> ¹²	Amsterdam <i>et al</i> ¹⁰	FDA public health advisory ⁸
Insomnia	Insomnia	Insomnia	Sleeplessness		Insomnia
Jitteriness	Jitteriness	Jitteriness	Jitteriness		
Irritability		Irritability		Irritability	Irritability, hostility
Unusual energy		Increased energy	Feeling euphoric, increased energy		
		Increased anxiety		Overanxious, Nervousness	Anxiety
		More severe panic attacks			Panic attacks
	Restlessness	Motor restlessness	Restlessness plus inability to remain still over five domains (at all, legs, lying, standing, sitting)	Restlessness/fidgetiness	Akathisia
		'Amphetamine speed-like response'			
				Trembling	
				Feeling on edge	
	Agitation		Shakiness	Inner shakiness	Agitation
				Anticipating the worst	
				Unable to relax	
				Easily startled	
					Impulsivity
	Diarrhoea				
			Palpitations		
			Limb sensations		
					Hypomania, mania

FDA, Food and Drug Administration.

more likely to cause symptoms of jitteriness/anxiety syndrome (Table 1) than placebo or diazepam. Limitations are small numbers ($n=52$) and unknown randomisation or concealment measures.

Beasley *et al*¹³ analysed data from a double-blind RCT ($n=706$) of fluoxetine (up to 80 mg/day) *v.* imipramine (up to 300 mg/day) and placebo. The primary aim was to examine efficacy of fluoxetine in treating depression and not to detect jitteriness/anxiety syndrome. However, participants were reviewed weekly to assess for symptoms of the syndrome (agitation, anxiety, nervousness, insomnia), which were recorded only if new or they had worsened from baseline. They reported significantly greater symptoms of the syndrome with fluoxetine (28%) compared with placebo (17%). There was a non-significant trend linking imipramine to more symptoms of jitteriness/anxiety syndrome than placebo. Treatment discontinuations because of the syndrome symptoms were: fluoxetine (5%), imipramine (5%) and placebo (0%), a statistically significant difference for both medications compared with placebo.

Beasley *et al*¹⁴ subsequently examined pooled data (total $n=746$) from three RCTs involving fluoxetine in depression. The primary focus of these trials was to examine efficacy of differing fluoxetine doses. Symptoms of jitteriness/anxiety syndrome (agitation, anxiety, nervousness, insomnia) were recorded weekly only if they were new or worsened during treatment. The trial employing lower daily doses (5, 20, 40 mg) reported statistically significant increases in jitteriness/anxiety syndrome symptoms for 5 and 20 mg, but not 40 mg compared with placebo. The two trials employing higher doses found a statistically significant increase of jitteriness/anxiety syndrome symptoms in the 40 and 60 mg groups but not the 20 mg group. The authors' opinion of a dose–response relationship between fluoxetine and activation, through increased activation at the highest doses, is open to debate – the trial incorporating 60 mg/day dosing had the highest placebo response and is contradicted by the inverse dose–response of the low-dose trial.

Toni *et al*'s naturalistic open study of 326 people with panic disorder over 3 years examined jitteriness/anxiety syndrome incidences with tricyclics (imipramine or clomipramine) and paroxetine.² Symptoms occurred in 16% of those on tricyclics and 7% of those on paroxetine. Limitations included high drop-out rates, selection bias (participants previously developing jitteriness on tricyclics received paroxetine), a lack of masking, operationalised definition of jitteriness/anxiety syndrome and placebo comparison.

Harada *et al* completed a retrospective case-note survey of people prescribed antidepressants looking specifically for jitteriness/anxiety syndrome symptoms in the FDA Public Health Advisory report⁸ (Table 1), in the first 3 months of treatment.¹⁵ Paroxetine, fluvoxamine, milnacipran, amoxapine, clomipramine and mianserin were implicated in producing jitteriness/anxiety syndrome symptoms. However, activation required only one symptom following treatment, with no baseline reference point. Information was obtained from case notes, introducing various biases. Therefore, it is unclear if symptoms were accurately ascertained and whether antidepressant medication was associated. Further evidence has chiefly implicated fluoxetine^{10,16–20} and imipramine.^{21–26} There is also evidence for jitteriness/anxiety syndrome with other tricyclics (clomipramine,^{11,27,28} dothiepin (dosulepin)²⁶ and desipramine,²² other SSRIs (sertraline (on dose titration rather than initiation)²⁹ and paroxetine)^{30,31} and the 5-HT_{1A} agonist buspirone,³² although less frequently than with imipramine.³³

Tollefson *et al* examined data from the US investigational new drug database.³⁴ New emergence or worsening of item 9 of the

Hamilton Rating Scale for Depression (HRSD) on psychomotor agitation, as a surrogate marker for jitteriness/anxiety syndrome, was compared across 31 placebo or comparator (tricyclic) controlled trials of fluoxetine treating depression. They found no significant difference between incidences of worsening psychomotor agitation between fluoxetine, tricyclics or placebo. However, most participants reported psychomotor agitation at entry and the HRSD item 9 may have been unable to detect changes. Other papers have reported no excess in jitteriness/anxiety syndrome symptoms on reboxetine³⁵ or sertraline³⁶ compared with placebo.

Few studies have compared jitteriness/anxiety syndrome incidence between antidepressants. Harada *et al*¹⁵ found no relation between antidepressant class and jitteriness/anxiety syndrome incidence. Beasley *et al*¹³ found no difference between fluoxetine and imipramine, and Tollefson & Saylor³⁴ found none between fluoxetine and tricyclics. Pohl *et al*²² suggested that there may be a greater risk with desipramine than imipramine, but small numbers were studied.

There is most evidence that imipramine and fluoxetine can cause jitteriness/anxiety syndrome. However, for both drugs evidence is contradicted by a minority of studies (level D). Evidence implicating other antidepressants is less abundant (level D). There is little robust evidence comparing rates of jitteriness/anxiety syndrome between different antidepressants (level D).

In which disorders has jitteriness/anxiety syndrome been reported?

Considering panic disorder with and without agoraphobia, Yeragani *et al*¹² found significantly increased rates of jitteriness/anxiety syndrome with imipramine compared with diazepam or placebo in an RCT in panic disorder. Lower rated evidence derives from naturalistic studies,² retrospective side-effect studies,²⁵ case series,²¹ single-blind trials^{11,27} and a double-blind trial with limited evaluation or comparison of jitteriness/anxiety syndrome symptoms.²³

Regarding jitteriness/anxiety syndrome in major depression, Beasley *et al*¹³ found significantly more symptoms in fluoxetine-treated participants with depression compared with placebo in an RCT (described above). Further evidence in SSRI-treated individuals with depression is provided by Beasley *et al*¹⁴ and Hu *et al*.³⁷ Stahl *et al*³⁵ found no significant difference between reboxetine and placebo in a summary of nine RCTs in treating people with depression but reboxetine has not been associated with jitteriness/anxiety syndrome in other disorders. Tollefson *et al*³⁴ also found no difference in agitation scores (taken from item 9 of the HRSD) between fluoxetine (20 mg) and placebo-treated groups of people with depression in their analysis of RCT data. These varying conclusions could be explained by a number of factors including differing methodologies (e.g. definitions of jitteriness/anxiety syndrome), differing medications and using data for purposes which it was not originally intended.

Less evidence exists for jitteriness/anxiety syndrome in other disorders. There is one retrospective analysis of RCT data in obsessive–compulsive disorder,²⁸ one case report in generalised anxiety disorder,³² a report of two cases in social phobia²⁴ and in a double-blind trial with limited evaluation of jitteriness/anxiety syndrome in agoraphobia, simple and mixed phobias.²³

Harada *et al*¹⁵ found no correlation with diagnosis of an anxiety disorder or major depressive disorder and jitteriness/anxiety syndrome incidence. They did find some positive correlation between 'tendency of Axis II diagnosis' (with abnormalities in any one of cognition, affectivity, interpersonal functioning and impulse control) and the syndrome.

In summary, there is most evidence that jitteriness/anxiety syndrome occurs in people with panic disorder (evidence level C). The evidence in major depression is contradictory (level D) and there is very little evidence beyond case reports that jitteriness/anxiety syndrome exists in obsessive–compulsive disorder, generalised anxiety disorder, social phobia and mixed or simple phobias (level D). No papers directly compared the rates of the syndrome between disorders.

What is the incidence of jitteriness/anxiety syndrome?

Published incidences of jitteriness/anxiety syndrome vary considerably (4–65%), through differing criteria for jitteriness/anxiety syndrome ‘caseness’, differing methods and times of collecting data and variations between cultures, disorders and medications implicated. Table 2 illustrates rates for each study where this could be calculated. Thus, predictions of incidence are at evidence level D.

Is there a known time course of jitteriness/anxiety syndrome?

Available evidence suggests jitteriness/anxiety syndrome has an early onset, but whether symptoms persist is unclear. From prescription event monitoring Edwards & Anderson³⁹ determined rates of symptoms for the first 2 months treatment with the SSRIs paroxetine, fluoxetine and fluvoxamine (Table 3). Although this methodology may be associated with underreporting, adverse events reported in the first month were greater for agitation, anxiety, hyperactivity and irritability for all three drugs, suggesting either remission of jitteriness/anxiety syndrome symptoms or excess treatment cessation among those affected. Only hypomania was increased in the second month, suggesting its aetiology may derive from a different mechanism to the main jitteriness/anxiety syndrome symptoms. Thus the contention of the FDA⁸ that hypomania and mania are components of jitteriness/anxiety syndrome requires further consideration. Ramos *et al*¹¹ found a short-lived 5–6 day syndrome with first day onset in an uncontrolled trial of imipramine in panic disorder. Yeragani *et al*¹² reported jitteriness symptoms peaking in week one and diminishing following week two. Aronson²¹ found a short-lived 3–13 day syndrome in panic disorder. Five of seven participants developing jitteriness/anxiety syndrome had no symptoms by week eight. Beasley *et al*¹⁴ calculated rates of symptoms by week from RCT data. Onset was in the first week, but persisted beyond the endpoint (week six). Hu *et al*³⁷ conducted a retrospective telephone survey of patients taking SSRIs for over 3 months, assessing if side-effects began within 2 weeks and whether these persisted beyond 3 months. High rates of insomnia (64%) and anxiety (71%) were found in the first 2 weeks. Both symptoms persisted with high prevalence at 3 months (56% and 49% respectively).

Table 2 Incidences of jitteriness/anxiety syndrome by paper

Paper	Incidence of jitteriness/anxiety syndrome	Level of evidence
Ackerman <i>et al</i> ²⁸	Clomipramine, 3% Fluoxetine, 4%	4
Amsterdam <i>et al</i> ¹⁰	33%	4
Aronson ²¹	32%	4
Beasley <i>et al</i> ¹³	Fluoxetine: any, 28% (discontinuation, 5%) Imipramine: any, 21% (discontinuation, 5%) Placebo: any, 17% (discontinuation, 1%)	4
Gorman <i>et al</i> ¹⁷	35%	4
Harada ¹⁵	4%	4
Hu <i>et al</i> ³⁷	Any, 19% (bothersome, 11%)	4
Lotufo-Neto <i>et al</i> ²⁷	5%	4
Louie <i>et al</i> ¹⁸	26%	4
Noyes <i>et al</i> ²⁵	20%	4
Perlis <i>et al</i> ¹⁹	Activation, 21% Anxiety, 15%	4
Pohl <i>et al</i> ²²	27%	4
Pohl <i>et al</i> ³⁶	0%	4
Pohl <i>et al</i> ³³	Imipramine, 45% Buspirone, 17%	4
Ramos <i>et al</i> ¹¹	27%	3B
Stahl <i>et al</i> ³⁵	Reboxetine: agitation, 4% (anxiety, 2%) Placebo: agitation, 4% (anxiety, 4%) No significant difference between groups	3B
Tollefson & Sayler ³⁴	Fluoxetine: any worse, 29% (substantially worse, 3%) v. placebo: any worse, 31% (substantially worse, 4%) Fluoxetine: any worse, 33% (substantially worse, 7%) v. tricyclic antidepressants: any worse, 29% (substantially worse, 6%) No significant group difference	2B
Toni <i>et al</i> ²	Tricyclic antidepressants, 16% Paroxetine, 7%	2C
Yeragani <i>et al</i> ¹²	44%	3B
Zajecka <i>et al</i> ³⁸	11%	3B
Zitrin <i>et al</i> ²³	18%	4

There is some evidence that jitteriness/anxiety syndrome has an early onset in the first 2 weeks (evidence level C). There is limited and contradictory evidence regarding persistence of the syndrome (level D).

What is the relationship between jitteriness/anxiety syndrome and therapeutic response?

Reports conflict on whether jitteriness/anxiety syndrome predicts therapeutic response. Ackerman *et al*²⁸ performed a retrospective data analysis of two RCTs (fluoxetine and clomipramine in obsessive–compulsive disorder) calculating risk ratios to determine whether early side-effects and demographic variables

Table 3 Prescription event monitoring data: incidence (per 1000 individuals) for selected adverse events in the first month of treatment compared with month 2³⁹

	Fluoxetine		Fluvoxamine		Paroxetine	
	Month 1	Month 2	Month 1	Month 2	Month 1	Month 2
Agitation	5.9	1.6	9.3	2.0	5.0	1.9
Anxiety	8.3	3.6	9.1	2.9	4.3	1.5
Hyperactivity	1.1	0.0	0.1	0.0	0.5	0.1
Irritability	0.6	0.4	0.1	0.8	0.5	0.1
Mania/hypomania	0.2	0.9	0.1	0.6	0.5	0.4

predicted outcome. Early nervousness predicted small increases in response to both clomipramine and fluoxetine. However, this was relatively rare and most responders did not experience it.

However, other reports suggest jitteriness/anxiety syndrome predicts a poor outcome. Gorman *et al*¹⁷ noted that no people developing jitteriness/anxiety syndrome responded to fluoxetine for panic disorder in a small uncontrolled study. Pohl *et al*²² reported individuals with panic disorder who developed the syndrome tolerated significantly less medication and a non-significant trend towards poorer response, but no significant interaction regarding dose of medication.

Jitteriness/anxiety syndrome has been linked to early treatment discontinuation. Noyes *et al*²⁵ cite 'overstimulation' as the main early side-effect causing treatment cessation (7 of 19 in the first 6 weeks) in their retrospective follow-up of panic disorder. Aronson²¹ found 13 participants dropped out because of intolerable symptoms in a naturalistic trial of 60 people. Neither of these trials had placebo or comparator drugs. Zitrin *et al*²³ alluded to a subgroup developing the syndrome who could not tolerate therapeutic doses of imipramine, but nevertheless improved on lower doses. No data were presented to verify this assertion.

There is conflicting evidence that jitteriness/anxiety syndrome predicts either an improved or poorer prognosis (level D). Limited evidence suggests people with panic disorder with the syndrome may tolerate only lower doses of tricyclic antidepressants without affecting outcome (level D). There is little evidence that it causes treatment cessation (level D).

Which management strategies are effective for jitteriness/anxiety syndrome?

Four management strategies were found for jitteriness/anxiety syndrome: initial slow titration from low doses of antidepressant, augmentation with benzodiazepines and symptomatic treatment with antipsychotics or beta-blockers.

In an open trial using alprazolam to treat those individuals developing the syndrome on fluoxetine, Amsterdam *et al*¹⁰ reported that it significantly reduced symptoms. However, biases are inherent in the open design and the possibility of spontaneous remission of the syndrome. Use of low initial doses and slow titration of antidepressants to prevent side-effects has not been evaluated specifically for jitteriness/anxiety syndrome. In an RCT, Pohl *et al*³⁶ investigated efficacy of sertraline in panic disorder. The syndrome was no more frequent with sertraline than with placebo. The authors believed this was through the low initial starting dose (25 mg/day), but the trial was not designed to assess this. Giesecke¹⁶ reported an individual with panic disorder developing jitteriness/anxiety syndrome on fluoxetine, managed successfully by reducing the dose to 1 mg/day and titrating up slowly over several months.

Pohl *et al*,²⁶ described two individuals with jitteriness/anxiety syndrome treated successfully with low doses of perphenazine. Lipinski *et al*⁴⁰ described five individuals with fluoxetine-induced akathisia, reported to be indistinguishable from jitteriness/anxiety syndrome. All improved with the addition of the beta-blocker propranolol. Evidence levels for either starting at a low dose of antidepressant, early augmentation with a benzodiazepine, symptomatic treatment with antipsychotics or beta-blockers are all low (level D).

What is the relationship of jitteriness/anxiety syndrome to akathisia?

No studies were designed to address the relationship between jitteriness/anxiety syndrome and akathisia. Harada *et al*'s¹⁵

retrospective study (described earlier) specifically looked for akathisia as part of their definition of jitteriness/anxiety syndrome. Of 31 individuals developing the syndrome, none had akathisia. Pohl *et al*²⁶ described two individuals with the syndrome responding to phenothiazines, which exacerbate akathisia. Lipinski *et al*⁴⁰ reported five people with fluoxetine-induced akathisia, which the authors believed indistinguishable from jitteriness/anxiety syndrome. Further case reports made no attempt to determine whether jitteriness/anxiety syndrome was distinct from akathisia.⁴¹ Overall, the little evidence that exists suggests jitteriness/anxiety syndrome is a separate entity from akathisia (level D).

What is the relationship between jitteriness/anxiety syndrome and suicide?

Tollefson *et al*⁴² performed a retrospective data analysis of 17 RCTs, comparing rates of suicidality (a suicidal act or ideation) and examining the temporal relation with defined side-effects, including activation. They found no significant relationship between activating side-effects and suicidality, nor any significant differences in rates of suicidality between the groups (fluoxetine, tricyclic and placebo). All data were gathered retrospectively from studies not designed to test this hypothesis, using measures such as item 3 of the HRSD to obtain information on suicidal ideation and adverse event data for suicidal acts. This may not give a complete or generalisable picture of events. During these trials it is not known whether a disproportionately high number of people developing the syndrome dropped out early, obscuring any relationship between suicidality and the syndrome.

Hammad pooled results from RCTs using SSRIs and atypical antidepressants (venlafaxine, nefazodone, mirtazapine and bupropion) in the treatment of children and adolescents. He calculated the relative risk of suicidality (suicidal ideation, acts or possible suicidal behaviour) between active arms and placebo. He found significantly increased relative risks of suicidality if symptoms of activation were present.⁴³ Again, caution is needed interpreting these results because of the *post hoc* analysis and multiple outcomes from data analysis in which jitteriness/anxiety syndrome and suicidality were not primary outcomes.

Subsequent to our initial search a further relevant study has been published. Perlis *et al*¹⁹ found a significant association between treatment-emergent agitation and emergent suicidal ideation, defined by item 3 of the HRSD, using trial data. Again, the study was not designed to assess rates of jitteriness/anxiety syndrome or suicidal ideation. It was an open, uncontrolled trial with no information on temporal relationships between emergence of suicidal ideation and activation. Suicidal ideation also related to worsening mood and it is unclear whether activation represented a genuine side-effect or a worsening general clinical picture. Remaining evidence on jitteriness/anxiety syndrome and suicidality is limited to case reports.⁴⁴ As yet there is no direct evidence to support an association of the syndrome and completed suicide, and currently only limited evidence to support the hypothesis that its symptoms are associated with greater suicidal acts or ideation (evidence level D).

Is there a genetic predisposition to jitteriness/anxiety syndrome?

Three studies examined genetic bases of agitation and motor activity as adverse events in antidepressant treatment, but there is no published work specific to genetic predispositions for jitteriness/anxiety syndrome.

Putzhammer *et al*⁴⁵ studied the 5-HTT (serotonin transporter) polymorphism in major depression, reporting LL homozygous carriers that were treated with SSRIs formed a distinct group having significantly higher night-time motor activity (compared with SS or SL) measured by actigraphy on day 5. These individuals had a trend towards greater movements during the day on the movement and activation scale, but no other symptoms pertaining to jitteriness/anxiety syndrome were addressed. In contrast to Putzhammer, Perlis *et al*⁴⁶ found that SS homozygous carriers had significantly more insomnia, agitation and a poorer response to treatment. Murphy *et al*⁴⁷ studied the 5-HT_{2A} receptor gene reporting that a single nucleotide polymorphism (T/C) had a significant impact on paroxetine side-effect and discontinuation rates (with no effect in a parallel mirtazapine treated group). Patients with the CC genotype had more frequent and severe adverse events and poorer adherence than other individuals. At present there is little evidence to link jitteriness/anxiety syndrome symptoms to known genetic polymorphisms (level D).

Discussion

In this systematic review we identified and examined all available scientific evidence relating to our predetermined questions on jitteriness/anxiety syndrome, finding a total of 107 relevant papers. A different approach that could be adopted in future would be to scrutinise systematically all RCTs of antidepressants for symptoms and symptom clusters developing early in treatment. The fact that there are no validated, or commonly used, measures for jitteriness/anxiety syndrome highlights how little objective evidence there is pertaining to it. Indeed, the terms commonly used such as 'jitteriness' and 'activation syndrome' are ill-defined and require clarification. Nevertheless, jitteriness/anxiety syndrome is frequently discussed in clinical guidelines^{4,5} and used to substantiate theories on neurotransmitter function.^{5,6} This presents a problem for the clinician, the psychopharmacologist and for any systematic review. How can the evidence for a syndrome that has not been clearly defined be reviewed with accuracy? Many papers reviewed could have been measuring phenomena irrelevant to jitteriness/anxiety syndrome. The lack of objective measures of activation, such as actigraphy, compounds this problem.

For consistency, we started from the contemporary viewpoint that jitteriness/anxiety syndrome exists,⁵ typically causes an anxiety-like overactivity state,^{8,23} starts early in antidepressant treatment²³ and has short duration.¹² In deciding whether individual symptoms also constituted jitteriness/anxiety syndrome, we took the view that measuring a symptom cluster was preferable, but would accept individual symptoms if they fitted into the classical descriptions of the syndrome (such as worsened anxiety, restlessness, etc.) and were described as commencing in the first weeks of treatment. This approach risks comparing different entities when comparing different papers, but allowed examination of the largest breadth of evidence. From this working definition, many antidepressant trials are likely to overlook jitteriness/anxiety syndrome; they usually start to measure symptoms and side-effects after a few weeks' treatment.

Although most reports of jitteriness/anxiety syndrome occur with imipramine and fluoxetine, there is no good evidence that it is more common in one drug than another. The fact that most reports relate to these drugs may be as a result of genuine pharmacological properties, that these drugs are or were previously the recommended medication for certain diagnoses or just the most commonly used medication in their classes. It is often suggested that jitteriness/ anxiety syndrome is

predominantly a side-effect of SSRIs. However, after much research interest in the 1980s, the association of the syndrome with tricyclics is now rarely discussed. Similarly with the SSRIs, after considerable interest in this syndrome following their introduction, there has been a decline in reporting as clinicians became more experienced with them. However, rather than being forgotten, jitteriness/anxiety syndrome continues to influence clinical guidelines on SSRIs despite the limited robust evidence. Trends in reporting have undoubtedly affected the evidence available.⁴⁸ Publication and reporting bias are issues that could not be examined here and their effect is unclear, whether over-reporting of positive cases when interest is high or underreporting by industry.

Jitteriness/anxiety syndrome was first described in individuals with panic disorder taking tricyclic antidepressants and thought to be confined to panic disorder or a clinical picture involving panic attacks.^{22,49} It may be that the perceived emphasis on the syndrome in panic disorder reflects reporting and research trends rather than any susceptibility conferred by panic. There is as much evidence that this syndrome occurs in major depression as other non-panic anxiety disorders.

Estimations of the incidence of jitteriness/anxiety syndrome vary widely. This may be as a result of factors addressed here, such as disorder treated and medication prescribed. Methodological differences will account for some of the variation. Examples would be: differing criteria for 'caseness' (including individual symptoms *v.* syndrome); variations in monitoring methods and times; different populations; and cultural variations. However, much of the variation may be as a result of the poor-quality data available. Most of the studies that looked for a jitteriness/anxiety syndrome were not generalisable to patient populations as a whole, or were retrospective using methods open to bias such as case-note reviews or telephone interviews. Studies that could yield robust rates for the syndrome, large RCTs, often do not assess individuals until 2 weeks have elapsed. Adverse effects are then usually obtained by 'non-probing' questions, which although having merits, may not identify a syndrome beginning and subsiding within the first week. It would therefore be advantageous for the identification of all early side-effects to assess people earlier in trials.

Available evidence supports the theory that this syndrome appears early in treatment, perhaps in the first week. This evidence is however weak. It is unclear how long jitteriness/anxiety syndrome persists. Some studies, especially those examining panic disorder, have found a short-acting syndrome.^{11,12,21} Others examining persistent side-effects in depression report jitteriness/anxiety syndrome symptoms persisting for several months.³⁷ There is no clear evidence of a syndromic difference with respect to differing disorders. It is more likely that methodological differences between studies account for this. Our own search strategy, acknowledging the current opinion that jitteriness/anxiety syndrome is an early side-effect and therefore including papers that look for early side-effects may have introduced biases. However, to review all side-effects occurring throughout treatment would have broadened the scope of this review to the point that our results would not reflect the issue in hand, the delineation of jitteriness/anxiety syndrome.

Despite being regularly discussed in reviews on anxiety disorders^{5,50-52} and being common practice, evidence for a slow titration of antidepressant or benzodiazepine augmentation is poor. Without valid instruments to quantify symptom severity, prospective studies have to rely upon a reduction in the incidence of this syndrome *per se* as an end-point. A further problem in studying the management of symptoms is the presumed short natural time course, such that any decrease in symptoms may

be as a result of the natural resolution of the syndrome. Studies researching this question in future will require a placebo control. Surprisingly, no study has determined whether patient education affects perceived severity of jitteriness/anxiety syndrome or associated discontinuation rates. This may impact upon persistence with medication if people are aware of the syndrome, its benign nature and short time course.

The question of whether jitteriness/anxiety syndrome is a prognostic factor for the response to medication remains unanswered. It is possible jitteriness/anxiety syndrome has different consequences in different disorders, but this has not been studied. The current consensus that the syndrome affects treatment outcomes by increasing discontinuation has little evidence to support it despite face validity. The possibility that people who continue treatment despite developing jitteriness/anxiety syndrome may achieve better treatment efficacy than those not developing the syndrome has still to be elucidated.

Despite the paucity of evidence addressing the issue of whether jitteriness/anxiety syndrome and antidepressant-induced akathisia are similar entities, this subject has generated some interest. Indeed, we found four reviews^{53–56} addressing antidepressant-induced akathisia (to varying degrees) which outnumber the number of papers providing evidence,^{15,26,40} totalling seven cases and one retrospective case-note survey. This is important as both antidepressant-induced akathisia and jitteriness/anxiety syndrome are postulated to be drivers for the disputed theory that suicide rates increase early on in antidepressant treatment.^{8,9,44}

No studies have addressed whether jitteriness/anxiety syndrome is related to completed suicide. This is not surprising given the rarity of completed suicide and difficulty defining jitteriness/anxiety syndrome. For suicidality, two of three studies identified suggested an association but had clear methodological limitations. Despite this, the FDA Public Health Advisory issued a warning in 2004 stating jitteriness/anxiety syndrome-like symptoms may be related to suicidality early in treatment. The medications listed were SSRIs, bupropion, venlafaxine and mirtazapine. There was no mention of tricyclic antidepressants despite the evidence of their association with the syndrome being comparable with that for SSRIs. Debate whether SSRIs induce an early increase in suicide rates is ongoing and not one covered by this review. However, there is a need to evaluate evidence objectively before comment, given the high media profile of this issue. There is also some perception among people that such an association could exist. For example, the 2004 UK Committee on Safety of Medicines Working Group on safety of SSRIs included a summary of questionnaire responses from people on paroxetine following a BBC documentary.⁵⁷ Suicidal ideas 'in the first few days' were reported by 8 of 38 respondents who provided information on the time course of events, although this data is prone to considerable selection and recall bias. Currently the presence of jitteriness/anxiety syndrome cannot be said to affect suicide rates or suicidality by itself, although more robust evidence may emerge if the syndrome is measured prospectively in large cohorts prescribed antidepressants.

If the hypothesis that variations in brain receptors and enzymes confer differing susceptibility to diseases is correct, then it follows that the same variations may well affect response to medications, including side-effects. However, it is likely that these effects will be spread across interactions of several genes and may vary with other environmental factors and epigenetic phenomena. These factors possibly contributed to the contradictory findings of Pützhammer *et al*⁴⁵ and Perlis *et al*⁴⁶ about which alleles of the 5-HT transporter gene conferred greatest risk for increased movement and agitation when treated with SSRIs.

Mechanisms

What are the mechanisms underlying jitteriness/anxiety syndrome? Many hypotheses exist but the most likely explanation is that the syndrome is caused by the increase in 5-HT function that SSRIs and other antidepressant drugs produce, which may impact on key postsynaptic receptors. Elevation in anxiety acutely after SSRIs and other serotonin-promoting agents can be seen in preclinical models and this can be blocked by antagonists of 5-HT₂ receptors.⁵⁸ It would be interesting to examine in future research whether drugs acting as antagonists at this receptor, such as the antidepressant mirtazapine or the atypical antipsychotic olanzapine, would attenuate the jitteriness/anxiety syndrome in humans.

Implications

Robust evidence regarding the aspects of jitteriness/anxiety syndrome we examined does not exist, in contrast with the prominence and influence the syndrome has in prescribing guidelines and clinical practice. This provides a mandate for further research into jitteriness/anxiety syndrome. In particular it is unclear which factors (e.g. diagnosis, medication class or genetics) are associated with increased risk. Neither are the ramifications of the syndrome clear, but poor adherence, non-response or indeed improved response are possible outcomes. We advocate further specific research into this clinically important area, leading both to a better understanding of the neurochemistry of antidepressants and to improved patient care.

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