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Comparative Risk for Harms of Second-Generation Antidepressants

A Systematic Review and Meta-Analysis

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Abstract

Background: Evidence indicates that only minor differences in efficacy exist among second-generation antidepressants for the treatment of major depressive disorder (MDD). However, a comprehensive assessment of both benefits and harms is crucial to evaluate the net benefit.

Objective: To review systematically the comparative harms of second-generation antidepressants for the treatment of MDD in adults by including both experimental and observational evidence.

Data sources: We searched MEDLINE®, EMBASE, PsychLit, The Cochrane Library and the International Pharmaceutical Abstracts from 1980 to April 2007. We manually searched reference lists of pertinent review articles and explored the Center for Drug Evaluation and Research database to identify unpublished research.

Study selection: Eligible study designs were trials and observational studies comparing one drug of interest with another.

Data extraction: Two persons independently reviewed abstracts and full-text articles. One investigator extracted relevant data. A senior reviewer checked data for completeness and accuracy.

Data synthesis: We included 104 experimental and observational studies. If data were sufficient, we conducted meta-analyses of randomized controlled trials on the relative risk of specific adverse events. Findings indicate that the spectrum of adverse events is similar. The frequency of specific adverse events, however, differed across drugs. Venlafaxine was associated with a significantly higher rate of nausea and vomiting than selective serotonin reuptake inhibitors. Compared with other drugs, paroxetine frequently led to more sexual adverse effects and bupropion to fewer such effects; mirtazapine and paroxetine was associated with more weight gain and sertraline with a higher rate of diarrhoea. Overall, however, these differences did not lead to different discontinuation rates. The evidence is insufficient to draw conclusions about rare but severe adverse events.

Conclusions: Adverse event profiles are similar among second-generation antidepressants. However, different frequencies of specific adverse events might be clinically relevant and influence the choice of a treatment.

Background

Results from systematic reviews and meta-analyses indicate that only modest differences in efficacy may exist among second-generation antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone and venlafaxine) for the treatment of patients with major depressive disorder (MDD).[1-4] However, to evaluate the net benefit of any treatment, a comprehensive assessment of both benefits and harms (i.e. the totality of possible adverse consequences of an intervention)[5] is crucial.

Although second-generation antidepressants have similar efficacy, they differ in pharmacological modes of action, affecting several adrenergic, dopaminergic, muscarinic, serotonergic and other receptors. Their mechanisms of action are poorly understood, and drawing direct relationships between receptor subtypes and adverse events is difficult; nonetheless, some adverse effects may correlate with a drug's suspected mechanism of action. For example, drugs with dopaminergic (dopamine receptor) and noradrenergic (mainly α and β receptor) activity, such as bupropion or venlafaxine, may have cardiovascular or peripheral vascular effects. Drugs with high potency effects on serotonin 5-HT_{2C} receptors may contribute to agitation or restlessness, and stimulation of 5-HT_3 receptors may lead to nausea, vomiting and sexual dysfunction.[6] Second-generation antidepressants are also associated with rare but severe adverse events such as suicidality, hyponatremia and seizures, that cannot be readily explained by pharmacological mode of action. Table I summarizes second-generation antidepressants, their modes of action and dosage details. Although randomized controlled trials (RCTs) are considered the gold standard to assess causal effects, they have been criticized for inadequacy for reliably assessing harms of interventions. In particular, sample sizes are often too small and the duration of clinical trials too short to detect rare but severe adverse events. Furthermore, patients may tolerate adverse events in the highly controlled environment of a clinical trial that would compromise adherence under 'real world' conditions.

Such limitations can be overcome by large, well conducted observational studies that have enough power to detect rare events and reflect situations of daily clinical practice.[7] Therefore, to assess the harms of any intervention comprehensively, ana-

Table I. Second-generation antidepressants, assumed modes of action and dosage range

Generic name	US trade name[a]	Mechanism of action	Dosage range (mg/d)	Low (mg/d)	Medium (mg/d)	High (mg/d)
Bupropion[b]	Wellbutrin®	Dopaminergic, noradrenergic	100–450	<187.5	187.5–362.5	>362.5
	Wellbutrin SR®	Dopaminergic, noradrenergic	150–400	<212.5	212.5–337.5	>337.5
	Wellbutrin XL®	Dopaminergic, noradrenergic	150–400	<225	225–375	>375
Citalopram[b]	Celexa®	Serotonergic	20–60	<30	30–50	>50
Duloxetine	Cymbalta®	Serotonergic, noradrenergic, dopaminergic	40–120	<60	60–100	>100
Escitalopram	Lexapro®	Serotonergic	10–20	<12.5	13–17.5	>17.5
Fluoxetine[b]	Prozac® Prozac Weekly® Sarafem®	Serotonergic	10–80	<27.5	28–62.5	>62.5
Fluvoxamine[b]	Luvox®	Serotonergic	50–300	<112.5	113–237.5	>237.5
Mirtazapine[b]	Remeron®	Serotonergic, noradrenergic	15–45	<22.5	22.5–37.5	>37.5
Nefazodone[b]	Serzone®[c]	Serotonergic, noradrenergic	200–600	<300	300–500	>500
Paroxetine[b]	Paxil® Paxil CR®	Serotonergic	10–50	<20	20–40	>40
Sertraline[b]	Zoloft®	Serotonergic	50–200	<87.5	87.5–162.5	>162.5
Trazodone[b]	Desyrel®	Serotonergic	300–600	<375	375–525	>525
Venlafaxine	Effexor®	Serotonergic, noradrenergic, dopaminergic	75–375	<150	150–300	>300
	Effexor XR®	Serotonergic, noradrenergic, dopaminergic,	75–225	<112.5	112.5–187.5	>187.5

a Trade names are for identification purposes only.

b Generic available for some dosage forms.

c Brand name product no longer available.

CR = controlled release; **SR** = sustained release; **XL/XR** = extended release.

lysts should examine both experimental and observational evidence.

The objective of this study was to assess the comparative harms of second-generation antidepressants commonly used by adult patients with MDD by systematically reviewing both experimental and observational evidence. It summarizes and updates findings of a comparative effectiveness review on second-generation antidepressants conducted for the Agency for Healthcare Research and Quality (AHRQ).[3]

Methods

Data Sources

To identify relevant articles, we searched MEDLINE®, EMBASE, PsychLit, the Cochrane Library and the International Pharmaceutical Abstracts; we used either Medical Subject Headings (MeSH) as search terms when available or key words when appropriate. We combined terms for adverse events ('adverse events', 'harms', 'drug reactions', 'toxicity') with 'major depressive disorder [MeSH]' and the 12 specific second-generation antidepressants

listed in the first paragraph of the previous section (with their respective trade names). We manually searched reference lists of pertinent review articles and editorials. In addition, we explored the Center for Drug Evaluation and Research database to identify unpublished research submitted to the US FDA. We limited the electronic searches to 'human' and 'English language'. Sources were searched from 1980 to April 2007.

In addition, the Scientific Resource Center at Oregon Health & Science University (supported by the AHRQ) contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations. We received dossiers from three pharmaceutical companies (Eli Lilly and Company, GlaxoSmithKline and Wyeth).

Study Selection

Two persons independently reviewed abstracts and full-text articles. Records were considered for exclusion if they did not meet pre-established eligibility criteria, as described in table II. Investigators resolved disagreements about inclusion or exclusion by consensus or by involving a third reviewer. A final decision was based on agreement of two of the three reviewers. A study was eligible for inclusion if it compared at least two medications of interest in adult patients with MDD over a period of at least 6 weeks. Outcomes of interest were general and specific adverse events and discontinuations because of adverse events. We included both experimental designs and observational studies. We limited observational studies to those with large sample sizes (≥100 patients).

Table II. Eligibility criteria

Category	Definition of criterion
Population	Adult inpatients and outpatients with major depressive disorder
Intervention	Bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone and venlafaxine
Study design	Experimental and observational head-to-head studies Minimum study duration: 6 wks Minimum sample size: none for experimental designs; n ≥100 for observational studies
Outcomes of interest	Overall rate of adverse events Discontinuation because of adverse events Specific adverse events (e.g. gastrointestinal symptoms, weight gain, dizziness and others) Severe adverse events (e.g. suicidality, hyponatremia, sexual dysfunction and others)

Data Abstraction

Trained reviewers abstracted data from each included study into structured forms and assigned an initial quality rating. We assessed the internal validity (quality) of trials based on pre-defined criteria developed by the US Preventive Services Task Force (ratings: good-fair-poor),[8] Deeks et al.[9] and the National Health Service Centre for Reviews and Dissemination.[10] Elements of quality assessment for RCTs included, among others, randomization and allocation concealment, similarity of compared groups at baseline, use of intention-to-treat analysis and overall and differential loss to follow-up. Items assessed for observational studies included selection of cases or cohorts and controls, adjustment for confounders, methods of outcomes assessment, length of follow-up and statistical analysis.

Studies that had a serious flaw in one or more categories were rated 'poor' and were excluded from the analyses. We did not rate the internal validity of post-marketing surveillances or *post hoc* data analyses. We also assessed external validity (generalizability) to identify effectiveness studies, which are studies with a great applicability to primary care populations.[11]

In addition to internal and external validity, we assessed the comparability of dosages. Because we could not find any clear definitions about equivalence of dosages among second-generation antidepressants in the published literature, we developed a roster of low, medium and high dosages for each

drug (outlined in table I). This classification, based on the interquartile dosage range, does not indicate dosage equivalence. We used this to detect gross inequalities in dosing that could affect the comparative risk for harms.

Data Synthesis

Because data on most outcomes of interest were insufficient to conduct meta-analyses, we synthesized the evidence on the majority of outcomes qualitatively. When data from RCTs were sufficient, we conducted meta-analyses of the relative risk (RR) of experiencing a specific adverse event. However, because of the lack of data on individual comparisons among individual selective serotonin reuptake inhibitors (SSRIs), we assessed the comparative risks of SSRIs as a class relative to other second-generation antidepressants. For each meta-analysis, we conducted a test of heterogeneity (I^2) and applied both a random and a fixed effects model. When high heterogeneity was present ($I^2 \geq 60\%$), we explored the reasons by conducting sensitivity analyses according to population characteristics, dosages or drug formulations. We report the results of random effects models; in all meta-analyses, results from random and fixed effects models were very similar.

When pooled dichotomous outcomes were statistically significant, we calculated numbers needed to harm (NNH) on the pooled risk difference. We assessed publication bias using funnel plots and Kendell's tests. However, given the small number of component studies in our meta-analyses, results of these tests must be viewed cautiously. Because we were concerned about residual confounding, we did not pool observational studies. All statistical analyses were conducted using StatsDirect Statistical Software programme, version 2.3.8 (StatsDirect LTD, 2004 [Cheshire, UK]) and STATA 9.1 (StataCorp, 2005 [College Station, TX, USA]).

Results

Figure 1 depicts search results and the screening of the literature. We analysed the comparative adverse events data from 83 head-to-head RCTs (81 double-blinded, two open-label) on >17 000 patients, along with data from 21 observational studies on >740 000 patients. Details of study characteristics, quality ratings and main findings of double-blinded head-to-head trials[12-101] and open-label trials[102-123] are described as table S3 and table S4, respectively (supplementary material ['Article Plus'] at http://drugsafety.adisonline.com).

The quality of adverse events assessment in RCTs differed greatly. Few studies used objective scales such as the UKU-SERS (Utvalg for Kliniske Undersogelser Side Effect Scale)[124] or the adverse reaction terminology from the WHO. Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Determining whether assessment methods were unbiased and adequate was often difficult. Rarely were adverse events pre-specified and defined. Short study durations and small sample sizes additionally limited the validity of adverse events assessment in

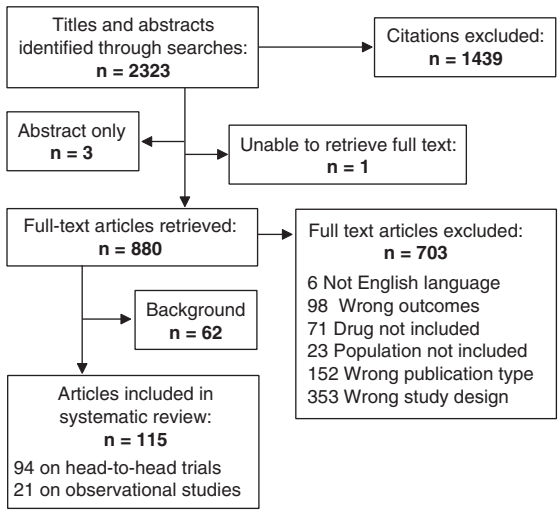

Fig. 1. Search results and screening of the literature.

many trials. Few RCTs were designed primarily to detect differences in adverse events.[12-17]

We have structured the following sections according to the FDA definitions of adverse events, distinguishing serious adverse events from other adverse drug reactions.[125]

Serious Adverse Events

The FDA defines 'serious adverse events' as any medical occurrence that results in death, is life threatening, requires inpatient hospitalization, results in persistent or significant disability or incapacity, or is a congenital birth defect.[125] The evidence on the comparative risk for most serious adverse events is insufficient to draw firm conclusions.

Mortality and Hospitalization

The evidence was insufficient to draw any conclusions about differences in mortality and hospitalization rates among second-generation antidepressants.

Suicidality

Sample sizes of efficacy trials were generally too small to be able to detect differences in the risk of suicidality (self-harm, suicide attempts, completed suicides) among the users of second-generation antidepressants. Six observational studies with data on >800 000 patients assessed the comparative risk of suicidality in patients treated with these agents.[102-107] In general, their results do not indicate that any particular drug of interest has an excess risk compared with that of other second-generation antidepressants. The only exception is a retrospective analysis of the UK General Practice Research Database. This study encompassed 54 events of >173 000 person-years and indicated a higher risk of suicidality for patients treated with venlafaxine than with citalopram (adjusted hazard ratio: 2.44; 95% CI 1.12, 5.31) or fluoxetine (adjusted hazard ratio: 2.85; 95% CI 1.37, 5.94).[107]

However, because these findings are based primarily on retrospective cohort studies, confounding by indication (i.e. patients who are at higher risk for suicide may be prescribed some medications rather than others) may lead to erroneous conclusions. None of these studies included data on escitalopram.

Sexual Dysfunction

Multiple studies assessed the comparative risk of sexual dysfunction (i.e. lack of sexual desire, pleasure, arousal and orgasm) among second-generation antidepressants.[14-17,26,45-52,117,126] The largest study was a Spanish prospective, observational study using the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) in 1022 outpatients treated with various antidepressants.[108] All patients had normal sexual functioning at study onset. Overall, 59% of patients experienced some type of sexual dysfunction. Among second-generation antidepressants, citalopram, paroxetine and venlafaxine had the highest incidence of sexual dysfunction (73%, 71% and 67%, respectively); mirtazapine and nefazodone had the lowest (24% and 8%, respectively). This study did not include data on bupropion, escitalopram and trazodone. In another study, findings of a cross-sectional survey of patients on second-generation antidepressants presented similar results.[109] Paroxetine had the highest rate of sexual dysfunction; nefazodone and bupropion had the lowest.

Sexual dysfunction was also commonly reported in efficacy trials. However, most studies did not report the use of targeted questions for sexual dysfunction. Therefore, patient-reported numbers might not reflect the true incidence. RCTs that assessed sexual dysfunction as a primary outcome[14-19] reported a high frequency of sexual dysfunction, similar to that from the Spanish observational study.[108]

Patients receiving paroxetine and sertraline frequently reported statistically significantly higher rates of sexual adverse effects than did patients in the active control groups.[19-24,127] In head-to-head

trials, bupropion consistently had the lowest rates of sexual dysfunction.[14-19]

Seizures

Evidence from controlled trials and observational studies is insufficient to conclude for or against an increased risk of seizures in patients taking any of the reviewed drugs, including bupropion. Two open-label trials[110,111] examined the rate of seizures during bupropion treatment. Both trials reported that the rate of seizures with bupropion was within the range of that for other marketed antidepressants.

A recent review of medical charts on 538 patients with deliberate self-poisoning with antidepressants reported that seizures were more common in patients with venlafaxine overdose than in patients with overdoses of either SSRIs or tricyclic antidepressants.[112]

Other Serious Adverse Events

A UK database analysis on fatal toxicity of second-generation antidepressants found venlafaxine to have the highest fatal toxicity rate (13.2 deaths per 1 000 000 prescriptions).[113] A retrospective review of the charts of 2428 nursing home residents did not detect differences in the risk of falls among fluoxetine, paroxetine and sertraline.[114]

The published literature includes numerous case reports of hyponatremia and inappropriate secretion of antidiuretic hormone,[128] hepatotoxicity associated with nefazodone[129] or serotonin syndrome[130] as rare adverse effects. Evidence from controlled trials and observational studies is insufficient to draw conclusions about the comparative risk of second-generation antidepressants for such events. Nevertheless, even if this evidence is considered weak, such findings might be important in the absence of studies with the methodological strength to account for rare adverse events.

General Tolerability

Overall, the adverse event profiles of second-generation antidepressants were similar. Nausea, vomiting, diarrhoea, dry mouth, sweating, headache, dizziness, sexual dysfunction and weight gain were commonly reported adverse events. On average, 63% of patients in efficacy trials experienced at least one adverse event during the course of a study. Most adverse events were mild (e.g. headache, sweating, dry mouth) and tolerable for patients. Others were more severe (e.g. nausea, diarrhoea, sexual dysfunction) and potentially threatened the continuation of treatments. A British prescription-event monitoring study indicated that fluvoxamine had the highest mean incidence rate of adverse events per 1000 patient-months compared with other examined SSRIs (fluvoxamine 17.6, paroxetine 7.6, fluoxetine 7.0 and sertraline 6.2).[115,116] In general, observational studies delineated the same adverse event profiles as efficacy trials, which indicates a good applicability of findings to primary care populations.

Discontinuation Rates

Discontinuation rates because of adverse events can be viewed as a crude measure of tolerability.[126,131] For clinical trials, such discontinuation rates should be interpreted in the context of overall loss to follow-up (i.e. the number of persons who were randomly selected, but did not reach the endpoint of the study)[132] because the quality of adverse events assessment differs greatly among studies. In efficacy studies, rates of discontinuation because of adverse events were not generally statistically significant. Overall, about 15% of patients treated with a second-generation antidepressant discontinued a study because of intolerable adverse events.

We conducted meta-analyses of data from efficacy trials to assess differences in the overall rates of discontinuation, discontinuation rates because of adverse events, and discontinuation rates because of

lack of efficacy of SSRIs as a class compared with other second-generation antidepressants (bupropion, duloxetine, mirtazapine, nefazodone, trazodone and venlafaxine; figure 2 a–c). Available data were insufficient to assess comparative discontinuation rates of individual SSRIs. Available data were also insufficient to determine discontinuation rates because of lack of efficacy for duloxetine, nefazodone and trazodone.

In our pooled estimates, the only statistically significant difference was a higher discontinuation rate because of adverse events for patients taking venlafaxine than for patients taking SSRIs (weighted mean: 12.1% vs 8.4%; RR 1.42; 95% CI 1.15, 1.75) [figure 2a]. This finding was balanced, however, by a numerically lower discontinuation rate because of lack of efficacy for venlafaxine than for other drugs (weighted mean: 3.9% vs 5.3%; RR 0.75; 95% CI 0.53, 1.05) [figure 2b]. Overall discontinuation rates did not differ significantly between venlafaxine and SSRIs (weighted mean: 25% vs 23%; RR 1.10; 95% CI 0.96, 1.26) [figure 2c].

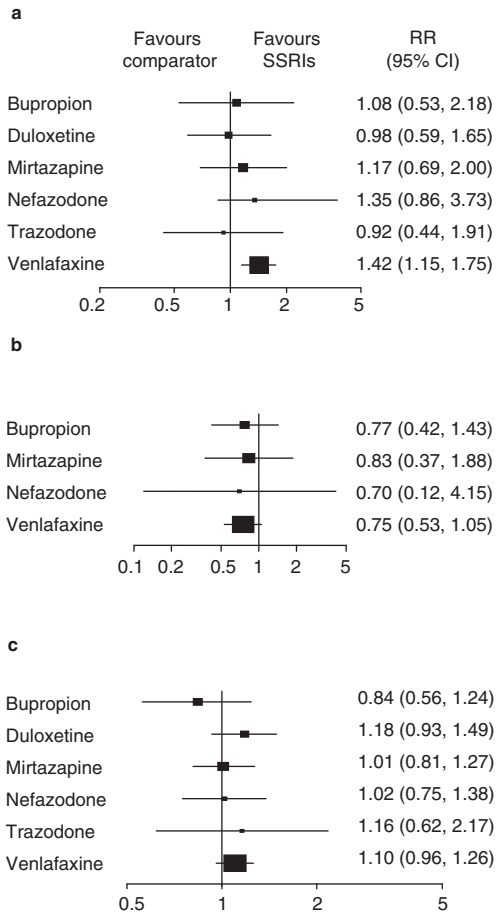

Fig. 2. Relative risk (RR) of discontinuation of comparator drugs vs selective serotonin reuptake inhibitors [SSRIs] (**a**) because of adverse events; (**b**) because of lack of efficacy; (**c**) RR of overall discontinuation.

Although adverse event profiles are similar among second-generation antidepressants, the incidence of specific adverse events differed between drugs. Differences were apparent primarily with respect to gastrointestinal adverse events and the risk of weight gain.

Gastrointestinal Adverse Events

In efficacy trials, venlafaxine had a consistently higher rate of nausea and vomiting than SSRIs. The percentage of patients reporting nausea or vomiting ranged from 6% to 48%.

Using data from RCTs,[25-41,133] we analysed the pooled RR of nausea and vomiting for venlafaxine compared with that for SSRIs as a class (figure 3). Venlafaxine had a statistically significantly higher rate of nausea and vomiting than SSRIs as a class (weighted mean: 34% vs 22%; RR 1.53; 95% CI 1.26, 1.86); the corresponding NNH is 9 (95% CI 6, 23). In other words, for every nine patients treated with venlafaxine rather than an SSRI, one additional patient will experience nausea and vomiting. These findings are consistent with a British prescription-event monitoring study.[115,116] Nausea and vomiting were the two most frequent clinical reasons for withdrawal in the first month of treatment for all drugs. Venlafaxine had the highest rate of nausea and vomiting per 1000 patient-months.

In a sensitivity analysis, we limited studies to those with extended-release formulations of venlafaxine.[27,29,31-34] Pooled results still detected a higher

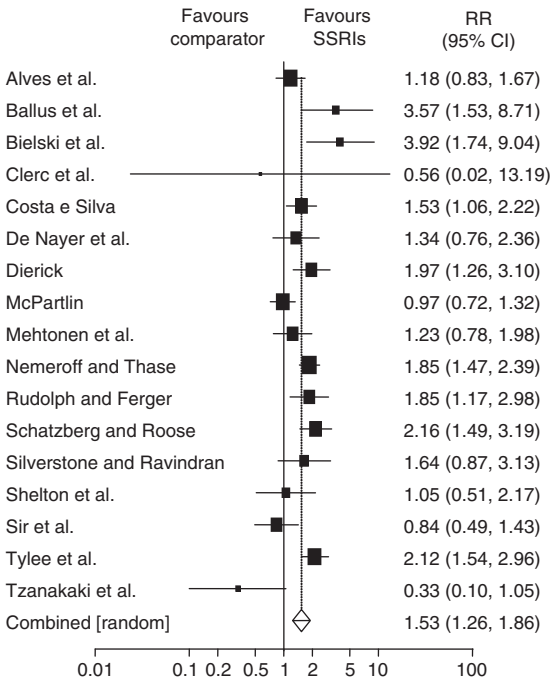

Fig. 3. Relative risk (RR) of nausea and vomiting with venlafaxine compared with selective serotonin reuptake inhibitors (SSRIs). Studies: Alves et al.,[35] Ballus et al.,[28] Bielski et al.,[29] Clerc et al.,[133] Costa e Silva.,[36] De Nayer et al.,[37] Dierick.,[25] McPartlin.,[33] Mehtonen et al.,[38] Nemeroff and Thase,[39] Rudolph and Feiger,[27] Schatzberg and Roose,[40] Silverstone and Ravindran,[31] Shelton et al.,[32] Sir et al.,[34] Tylee et al.,[26] Tzanakaki et al.[41]

risk of nausea and vomiting for venlafaxine extended release than for SSRIs, but statistical significance was lost (RR 1.38; 95% CI 0.93, 2.05)

In efficacy studies, sertraline frequently led to higher rates of diarrhoea than comparator drugs (bupropion, citalopram, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, venlafaxine).[19,21-24,38,42-50] The mean incidence was 8 percentage points (95% CI 3, 11) higher than with comparator drugs. This finding is consistent with results from a prospective Dutch cohort study of 1251 patients followed up to 12 months. Diarrhoea occurred more frequently in the sertraline group than with other SSRIs (fluoxetine, fluvoxamine, paroxetine; $p < 0.05$).[117] No differences in gastrointestinal adverse events were obvious among other second-generation antidepressants.

Changes in Weight

Studies comparing mirtazapine with other second-generation antidepressants consistently reported higher weight gains for mirtazapine than for comparator drugs.[51-57] In two RCTs, these differences reached statistical significance.[56,57] Mean weight gains ranged from 0.8 kg to 3.0 kg after 6–8 weeks of treatment. However, standard deviations of these changes were large, suggesting a high variability of weight gains among patients on mirtazapine.

A 32-week acute- and continuation-phase trial that assessed differences in weight changes among patients treated with fluoxetine, paroxetine and sertraline,[58] found that patients taking paroxetine had a significantly greater mean weight change (+3.6%) than those taking fluoxetine (−0.2%; $p = 0.015$) or sertraline (+1.0%; $p < 0.001$).

Cardiovascular Adverse Events

Efficacy trials infrequently assessed cardiovascular outcomes. In two RCTs, one comparing venlafaxine with sertraline[34] and one venlafaxine with fluoxetine,[39] statistically significant increases in supine diastolic blood pressure and supine pulse rate were detected for venlafaxine compared with fluoxetine.

A *post hoc* analysis of six RCTs (published and unpublished) comparing duloxetine with fluoxetine or paroxetine did not find any statistically significant differences in supine systolic or diastolic blood pressure.[118]

Other Adverse Events

Trazodone was associated with an approximately 16% (3% less to 36% higher) higher incidence of somnolence than comparator drugs (bupropion, fluoxetine, mirtazapine, paroxetine, venlafaxine).[51,59-63] Whether this finding can be extrapolat-

ed to comparisons of trazodone with other second-generation antidepressants remains unclear.

Discussion

To our knowledge, our systematic review is the first to incorporate both experimental and observational evidence to assess the comparative risks of harms associated with second-generation antidepressants. Observational studies are needed to assess the risk of harms because RCTs are often too limited by sample sizes and study durations to gauge the risk of rare adverse events.

Our systematic review synthesized findings from 83 trials and 21 observational studies with data on >950 000 patients. Overall, the spectrum of adverse events was similar between different second-generation antidepressants.

However, individual drugs differed in the frequencies of specific adverse events. For example, venlafaxine was associated with a higher rate of nausea and vomiting than were SSRIs as a class. In addition, compared with other second-generation antidepressants, paroxetine frequently led to higher, and bupropion to lower, rates of sexual dysfunction; mirtazapine and paroxetine led to higher weight gains, and sertraline to higher rates of diarrhoea. Overall, these differences did not lead to different discontinuation rates.

For some patients, the frequency of specific adverse events might be clinically important. For example, the choice of an agent with a low rate of sexual dysfunction might increase adherence in patients who consider sexual dysfunction an intolerable adverse event. People with cardiovascular risk factors should probably avoid agents that can increase blood pressure. Likewise, drugs associated with a high rate of diarrhoea or weight loss could be contraindicated for emaciated patients or patients with low body mass index because of eating disorders.[134] However, no evidence exists that any second-generation antidepressant leads to better or worse outcomes than others in patients with such comorbidities.

Except for sexual dysfunction, similar rates of adverse events were reported between observational studies and clinical trials. This suggests that, despite the fact that RCTs enrol highly selected patients, findings on harms can be extrapolated to primary care populations.

Our study has several limitations. Evidence on the comparative risk for some rare but severe adverse events – specifically suicidality, hyponatraemia, seizures or serotonin syndrome – was insufficient to draw firm conclusions. The risk of such harms should be considered during any course of treatment with a second-generation antidepressant. Recent findings have raised concerns about possible under-reporting or misclassification by drug manufacturers of adverse events such as suicidality.[135] We had no way to account for any systematic misstatements of severe adverse effects.

Furthermore, the quality of adverse event assessment differed greatly between studies: reporting was often poor and adverse events were rarely pre-specified and assessed using an objective scale. Considerable under-reporting, especially of 'embarrassing' adverse events such as sexual dysfunction, is certainly conceivable.

Finally, the evidence was too sparse to assess the comparative risk of harms for all 66 possible comparisons between second-generation antidepressants. In all of our meta-analyses, it was necessary to make comparisons of SSRIs as a class with other second-generation antidepressants. Because individual trials did not indicate substantial differences with respect to nausea or vomiting and discontinuation rates between SSRIs, we felt comfortable to pool them as a class. With the advances of new statistical techniques (e.g. network meta-analysis[136]), lack of direct head-to-head comparisons might, at least partially, be overcome in the future.

Even though we have included observational studies in our review, most of our data stem from efficacy trials. Although rates of specific adverse events were similar between observational studies and RCTs, the ways that specific adverse events may affect adherence in real-world settings remains unclear. Conceivably, patients in clinical trials are more motivated to endure adverse events than 'average' patients in primary care settings. Large, well conducted observational studies are needed to assess reliably the comparative risk of second-generation antidepressants with respect to rare but severe adverse events and adherence. Furthermore, these studies need to evaluate whether potentially vulnerable patient groups, such as elderly patients or patients with chronic diseases, face an excess risk of severe adverse events with second-generation antidepressants.

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