In Review

Metareview on Short-Term Effectiveness and Safety of Antidepressants for Depression: An Evidence-Based Approach to Inform Clinical Practice

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Objectives: To examine the available scientific literature for answers to clinically relevant questions regarding the effectiveness and tolerability of antidepressant drugs (ADs) for the acute phase treatment of depression and to assess the degree to which the literature supports the findings.

Methods: We used several sources to identify primary reviews: MEDLINE (1955 to April 2006), EMBASE (1980 to April 2006), PsycINFO (1980 to April 2006), and the Cochrane Library 2006 Issue 1. Additional searches were also carried out on the following databases of the National Health Service Centre for Reviews and Dissemination: Abstracts of Reviews of Effects, Health Technology Assessment, and Turning Research into Practice. We also searched the National Institute of Health and Clinical Excellence guidance website. We carried out a metareview of selected high-quality systematic reviews of short-term pharmacologic interventions with ADs for major depression. To assess efficacy, we followed the hierarchy of evidence proposed by the Centre for Evidence Based Medicine (Oxford), including only reviews of randomized controlled trials. To assess tolerability, we also considered observational data when randomized evidence was not available.

Results: There was randomized evidence that ADs are efficacious in primary care settings and that there may be small, but clinically important, differences in efficacy between ADs. There was no good evidence that an AD combined with an antipsychotic is superior to AD monotherapy in cases of psychotic depression or that intravenous administration leads to more rapid response. There was evidence that monoamine oxidase inhibitors are superior to tricyclic antidepressants, but not to selective serotonin reuptake inhibitors (SSRIs), in treating atypical depression. There is some evidence of harm related to the use of SSRIs in pregnancy but not to their use when breastfeeding. There is evidence that SSRIs may increase suicidal thoughts, but not actual suicide, in early-phase therapy.

Conclusions: We found a substantial body of evidence regarding the benefits and harms of ADs in the treatment of depressive disorder. Nonetheless, there remains considerable residual uncertainty. The evidence is inadequate for generally applicable recommendations; in most cases, the balance between risks and benefits will need to be considered for individual patients. Clinicians should also be guided by the recommendations and warnings issued by drug regulatory authorities.

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Clinical Implications

- ADs are efficacious in patients with depressive disorder in primary care settings.
- There may be small, but clinically significant, differences in efficacy among ADs.
- An AD combined with an antipsychotic is not clearly superior to AD monotherapy for psychotic depression.
- IV administration of ADs does not lead to more rapid response.
- MAOIs may be superior to TCAs, but not to SSRIs, in cases of atypical depression.
- There is some evidence of harm when SSRIs are used during pregnancy but not when they are used during breastfeeding.
- There is evidence that SSRIs may increase suicidal thoughts, but not actual suicide, in early-phase therapy.

Limitations

- There is evidence of publication bias in trials of ADs.
- Most studies included in systematic reviews were short-term and focused exclusively on improvement in depressive symptoms.
- Although effects on depressive symptoms are clear, effects on functional status and health-related quality of life outcomes are usually not reported.

Key Words: *depression, antidepressant, systematic review, efficacy, effectiveness, tolerability, suicide, breast feeding, pregnancy, atypical depression*

Robust evidence suggests the clinical efficacy of treatment with ADs in the management of moderate-to-severe unipolar major depression in adults. Month by month, the scientific literature offers new insights on existing clinical uncertainties.

This study was designed to answer some selected relevant questions about clinical outcomes of AD use in daily practice according to an evidence-based medicine approach. We conducted a metareview of high-quality systematic reviews of short-term pharmacologic interventions with ADs for major depression. The main aim was to examine the available scientific literature for answers to clinically relevant questions and to present a summary of the findings on the effectiveness and tolerability of ADs for the treatment of depression.

Method

We conducted a metareview of all available systematic reviews of the evidence. This method is not as intensive as a primary systematic review of a specific intervention for a defined clinical disorder, but it has been used to provide a useful overview of a large clinical area.[1] This metareview focuses on treatment with ADs for acute major depression. To assess the efficacy of AD treatment, we followed the hierarchy of evidence proposed by the Centre for Evidence Based Medicine (Oxford) and included only reviews that were rated 1A.[2] Level 1A refers to systematic reviews of RCTs because they provide the most reliable evidence for efficacy and tolerability. To assess tolerability, we also considered observational data when randomized evidence was not available.

Search Strategy

We used the search strategy used for the last update of *BMJ Clinical Evidence*.[3] We used several sources to identify primary reviews: MEDLINE (1966 to April 2006), EMBASE (1980 to April 2006), PsycInfo (1980 to April 2006), and the Cochrane Library 2006 Issue 1. Additional searches were carried out on the following databases of the NHS Centre for Reviews and Dissemination: Abstracts of Reviews of Effects, Health Technology Assessment, and Turning Research into Practice. We also searched the National Institute of Health and Clinical Excellence guidance website.[4] Abstracts of studies retrieved in the search were assessed independently by 2 reviewers.

Results

Main Findings and Interpretation

Research findings were interpreted in the context of implementing effective treatment strategies that used ADs for acute treatment of depression in daily, real-world clinical practice. We present results narratively, focusing on several specific and controversial clinical issues: ADs compared with placebo in primary care; the comparative efficacy of ADs; treatment of psychotic depression; IV administration of ADs; treatment of atypical depression; maternal use of SSRIs, pregnancy outcomes, and breast-feeding; and ADs and suicide.

What Is the Efficacy of ADs Compared With Placebo in Primary Care?

Randomized trials (and, therefore, systematic reviews) of ADs usually include more patients from specialist outpatient facilities than from primary medical care,[5] and concern has been expressed about the relevance of secondary care studies to primary care patients.[6] It is usually accepted that placebo-controlled trials are still required for new ADs[7]; these also provide an estimate of absolute efficacy. We identified one systematic review of the efficacy of ADs, compared with placebo, in treating depression in primary care settings.[8] The results of this study confirm that both TCAs and SSRIs are significantly more effective than placebo for both event-like and continuous outcomes. Fifteen RCTs including 890 participants were found in SSRI studies and 596 in TCA studies, with 1267 patients on placebo. Two trials studied sertraline, 3 studied escitalopram, and 1 studied citalopram. Two trials studied dothiepin, 4 studied amitriptyline, 2 studied mianserin, and 3 studied imipramine. Ten of the 15 studies were identified as having a competing interest. For depression scores, the standardized mean difference for TCA compared with placebo was –0.42 (95%CI, –0.55 to –0.30). The RR for improvement with a TCA was 1.26 (95%CI, 1.12 to 1.42); with an SSRI, the RR was 1.37 (95%CI, 1.21 to 1.55). The NNT for 1 improved patient ranged from 3 to 4 for the TCA studies that were statistically significant, and the NNT was 6 for SSRIs. In an analysis of 5 studies that had treatment group scores of < 8 on the HDRS, the weighted mean difference was –3.68 (95%CI, –5.89 to –1.47). An asymmetrical funnel plot of the TCA studies suggested that there may be some publication bias, and this highlights once more the risk of dealing only with published studies when systematically reviewing the literature. The RR for adverse effects leading to study withdrawal for TCAs was 2.35 (95%CI, 1.59 to 3.46); for SSRIs, it was 2.01 (95%CI, 1.1 to 3.7). The results of this review apply to major depressive disorder, suggesting that treating major depression with ADs is appropriate in primary care, although there have been concerns about prescribing Ads in primary care for minor depressive disorder.[9,10] The primary trials included in the review were small Phase III trials conducted by the pharmaceutical industry; they included patients with both major and minor depression and were usually of short duration (typically 6 to 8 weeks).

It is known that patients in primary care settings have a range of depression severity, and this should be taken into account when dealing with the generalizability of these study results to primary care.[11] The appropriate treatment of minor depression, for instance, is uncertain. In a 1-year follow-up cohort study of outcomes and predictors of outcome among patients with minor and subsyndromal depression, major depression, and no depression, patients with minor or subsyndromal depression had intermediate depressive and functional outcomes.[12] After controlling for demographic characteristics, patients with minor or subsyndromal depression had a 5.5-fold risk for major depression at 1 year, compared with patients not suffering from depression. At present, UK guidelines from the NICE recommend a stepped care approach,[13] according to which ADs should not be used for the initial treatment of mild depression because the risk–benefit ratio is poor, and to consider a watchful waiting intervention for patients with mild depression who may recover with no intervention. Although it is possible—although unknown—that early treatment of mild illness could prevent progression to major depression, this approach is recommended for patients with recurrent illness, especially when they have previously been AD-responsive. Further research is needed on these groups of patients, in addition to longer and larger trials of low-dose TCAs.[14]

Are All ADs Really the Same?

We found 2 systematic reviews summarizing the comparative evidence for ADs in major depressive disorder. The first review evaluated comparative data on the efficacy and tolerability of commonly prescribed second-generation ADs (SSRIs, bupropion, duloxetine, mirtazapine, and venlafaxine).[15] Overall, these trials reported similar outcomes among the 6 SSRIs. Pooling together the 6 studies (774 patients) that compared paroxetine with fluoxetine and classified treatment response according to HDRS scores suggested

Abbreviations used in this article

AD	antidepressant drug
CI	confidence interval
FDA	Food and Drug Administration
HDRS	Hamilton Depression Rating Scale
IV	intravenous
LBW	low birth weight
MAOI	monoamine oxidase inhibitor
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Clinical Excellence
NICU	neonatal intensive care unit
NNT	number needed to treat
RCT	randomized controlled trial
RR	relative risk
SCN	special care nursery
SMD	standardized mean difference
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
TCA	tricyclic antidepressant

that there was no statistically significant difference in the response rate between fluoxetine and paroxetine (RR 1.09; 95%CI, 0.97 to 1.21). This review also identified 5 studies (1190 patients) that compared fluoxetine with sertraline. Although no individual trial reported statistically significant findings, pooled results suggested a modest additional treatment effect for sertraline when compared with fluoxetine (RR 1.10; 95%CI, 1.01 to 1.22).

The second review compared fluoxetine, the most widely studied of the newer ADs, with each individual AD.[16] Instead of using a standard hypothesis-testing approach, this analysis used a more conservative approach based on noninferiority and estimated relative efficacy, with 99%CI. A total of 58 studies compared fluoxetine with TCAs, 9 studies compared it with heterocyclics, 22 compared it with SSRIs, and 44 studies compared it with other newer ADs. Analysis of efficacy was based on 4494 patients treated with fluoxetine and 4817 with an alternative AD. When dichotomous and continuous outcomes were considered, no statistically significant difference were found either between fluoxetine and individual TCAs or between fluoxetine and individual heterocyclics (that is, mianserin and maprotiline). Treatment with sertraline was more likely to produce response than treatment with fluoxetine (RR random effects 1.19; 99%CI, 1.02 to 1.38; NNT = 13; 99%CI, 8 to 100), although no difference was observed on continuous outcomes (SMD random effect 0.10; 99%CI, –0.05 to 0.25). Similarly, treatment with venlafaxine was significantly more effective in terms of producing response than was treatment with fluoxetine (RR random effects 1.17; 99%CI, 1.03 to 1.33; NNT =15; 99%CI, 9 to 50), but there was no significant difference on continuous outcomes (SMD random effect 0.11; 99%CI, –0.03 to 0.26). Some caution is needed when interpreting these results. The conditions within efficacy trials can be very different from the world of practice where an individual clinician needs to make treatment decisions based on clinically meaningful outcomes. The first nonrandomized phase of the STAR*D study is a good example.[17] The study enrolled outpatients with nonpsychotic depression at 23 psychiatric and 18 primary care sites, and of the 4041 potentially eligible patients, 2876 were eligible for analysis. All participants began with a course of up to 14 weeks of citalopram as a representative SSRI. The drug was administered according to a treatment manual that allowed individualized management of dosages within a preplanned schedule. The STAR*D primary outcome was pragmatic—to achieve remission from depression rather than partial improvement—and the overall remission rate was 27.5% (n = 790). These figures are similar to remission rates found in other studies; however, they are far from the results expressed as rates of response in the great majority of efficacy RCTs. Additional studies with other AD medications are needed to determine whether these findings are generalizable to other AD medications. Nevertheless, this is the approach to follow to obtain new and reliable evidence that will really inform clinical practice and help develop personalized care.[18]

In the systematic review by Cipriani et al,[16] the comparison between fluoxetine and individual heterocyclics or SSRIs did not reveal statistically significant differences; among newer ADs, only pramipexole was less well tolerated than fluoxetine, as indicated by failure to complete the trial for any reason (RR random effects 0.19; 99%CI, 0.04 to 0.84 and NNT = 3; 99%CI, 2 to 7). However, the UK MHRA recently has assessed the evidence for the safety of venlafaxine and has issued an alert about the potential for cardiotoxicity and toxicity in overdose with venlafaxine.[19] This illustrates that tolerability profile is crucial in guiding the choice of an AD and that caution is needed when prescribing ADs. In 2004, concerns about the safety of venlafaxine led to its restriction to specialist initiation and to contraindications in patients with heart disease.[13] In retrospective analyses from the United Kingdom reporting the rate of AD overdose deaths per million prescriptions, the MHRA found that the rate for venlafaxine was higher than that for SSRIs (but lower than that for TCAs). However, the UK government agency reports that there is epidemiologic evidence that venlafaxine is prescribed to patients with a higher preexisting suicide risk, compared with patients prescribed SSRIs.[20] Considering that fatal cardiotoxicity is very rare but that the risk may be increased in those with cardiac disease, the MHRA warns that venlafaxine is contraindicated in patients with a high risk of a serious cardiac ventricular arrhythmia (for example recent myocardial infarction) and in patients with uncontrolled hypertension. Regular measurement of blood pressure is recommended for patients receiving venlafaxine.[13]

Psychotic Depression

Although only a minority of patients with major depression experience psychotic symptoms, psychotic depression is a very important clinical entity because it is marked by greater severity, greater incapacity, and longer duration of episodes than is nonpsychotic depression.[21] In the pharmacotherapy of psychotic depression, it is unclear whether it is better to start with an AD alone or to combine it with an antipsychotic. One systematic review compared the clinical effectiveness of different pharmacologic strategies for people with psychotic depression.[22] This review identified only 10 RCTs.

The main clinical finding was that there is no evidence that the combination of an AD and an antipsychotic is more effective than an AD alone. The authors found 2 RCTs in which the combination of an AD and an antipsychotic was compared with AD monotherapy. Pooling these studies did not show a statistically significant difference between a TCA plus an

antipsychotic and a TCA alone (RR 1.44; 95%CI, 0.86 to 2.41; $P = 0.16$). Similar findings were retrieved by pooling studies comparing the combination of an AD and an antipsychotic with an antipsychotic alone together with the studies comparing an AD alone with a placebo. This gave a statistical difference favouring treatment with an AD (4 RCTs; RR 2.06; 95%CI, 1.41 to 3.00), which contrasts with American Psychiatric Association and NICE guidelines that recommend a combination strategy as first-line treatment for individuals with psychotic depression.[13,23]

Considering that antipsychotics are associated with troublesome adverse effect profiles (such as extrapyramidal side effects, hyperprolactinaemia, anticholinergic effects, weight gain, cardiotoxic effects, and metabolic syndrome), whether or not to use an antipsychotic is an important clinical issue. An evidence-based approach to the management of these patients should consider AD monotherapy initially and then a combination of AD and antipsychotic, if no response is achieved.

Is There a Rationale Supporting IV Administration of ADs?

Although treatments for depression are widely used, debate persists about a substantial delay between the start of an AD regimen and full clinical effect.[24,25] IV administration of ADs has been supposed to be an option for potentially more rapid onset of action, especially for drugs that undergo first-pass hepatic metabolism, such as some TCAs (for example, clomipramine and doxepin). Further, specific patient populations, such as medically ill patients, patients with gastrointestinal tract problems, and patients undergoing surgery, may be particularly suited for intravenously administered ADs. Even though this practice has received little attention in the United States, it has received considerable interest in Europe, especially with regard to inpatients during the first few days of admission.

One systematic review[26] found 10 RCTs in which IV ADs were used to treat depressive symptoms: 5 studies compared IV clomipramine (the most widely studied IV AD) with oral clomipramine or placebo; 3 studies compared IV citalopram (the only SSRI available in an IV formulation) with oral citalopram or viloxazine; 1 study compared IV maprotiline with oral maprotiline, and 1 study compared IV amitryptiline with oral amitryptiline. A metaanalysis was not conducted, and in general, IV administration was not associated with shortened onset of AD action or with an increase in side effects. However, the general issue about whether or not ADs have clinically important early effects has considerable significance for physicians and patients and also for understanding the pathogenesis of depressive disorders. Recently, one systematic review and metaanalysis was carried out with SSRIs in patients suffering from unipolar depression to test the hypothesis of delayed, compared with early, AD action.[25] The question of early onset of SSRI effects can be strategic because there are many placebo-controlled RCTs investigating the treatment of depression with SSRIs; these studies typically have a similar design that uses standardized rating scales with repeated assessments, usually on a weekly basis. The review included 50 RCTs with 6153 participants randomized to receive one SSRI and 3968 to receive placebo. Pooled estimates of treatment effects according to depressive symptom rating scales were calculated for weeks 1 through 6 of treatment. Using a statistical best-fitting model for early treatment response, Taylor and colleagues[25] found that treatment with SSRIs rather than placebo was associated with clinical improvement by the end of the first week of use (estimate of treatment effect –0.17; 95%CI, –0.13 to –0.21; $P < 0.001$; 28 RCTs and 5872 participants). Consistently, secondary analyses indicated an increased chance of achieving a 50% reduction in HDRS scores by 1 week with SSRI treatment, compared with placebo (RR 1.64; 95%CI, 1.2 to 2.25). That this review found some evidence that treatment with SSRIs is associated with symptomatic improvement in depression by the end of the first week of use could, in many cases, undermine the rationale for prescribing IV ADs.

Is Atypical Depression Preferentially Responsive to Treatment With MAOIs?

The origin of the concept of atypical depression as a distinct subtype is based on a reported preferential response to one class of ADs, the MAOIs. The preferential response to MAOIs is now part of accepted wisdom in clinical psychiatry, even though the varying definitions of atypical depression used before the inclusion of operational criteria in the DSM-IV make it difficult to interpret research findings.

One recent review compared the clinical effectiveness of pharmacologic treatments for patients with atypical depression.[27] It found a mean effect size of 0.45 (95%CI, 0.35 to 0.60) for a comparison of MAOIs with placebo (4 RCTs, 250 participants). However, there was some heterogeneity between comparisons (that is, MAOIs and placebo), possibly due to one study that showed a very high response rate difference between phenelzine and placebo (25/30, or 83%, with phenelzine; 5/26, or 19%, with placebo). The effect size for MAOIs when compared with the imipramine (4 RCTs, 236 participants) was 0.27 (95%CI, 0.16 to 0.42), reflecting a statistical superiority of MAOIs over TCAs. Only 3 double-blind RCTs provided a direct comparison of MAOIs and SSRIs. These data showed that phenelzine or moclobemide were not superior to SSRIs in terms of response rates (85/127, or 67%, with MAOIs; 90/138, or 65%, with SSRIs) and effect sizes (0.02; 95%CI, –0.10 to 0.14; 265 participants). Because of the rather small number of subjects, these findings should be interpreted cautiously. There may be important unpublished

work that could not be considered, leading to a publication bias. A serotonin hypothesis for atypical depression has been suggested.[28]

In this field, most clinical studies have been conducted on traditional MAOIs (for example, phenelzine). More selective and less toxic MAOIs (such as moclobemide) are now available and approved by international regulatory agencies; however, there are only a few RCTs comparing the efficacy of reversible MAOIs with other ADs or placebo for atypical depression. In many cases, SSRIs have shown similar efficacy to MAOIs; however, there is insufficient randomized evidence to determine the efficacy of SSRIs in patients with atypical depression.

Is There a Relation Between Maternal SSRI Use and Newborns' Prematurity or Malformation?

All SSRIs, as well as venlafaxine, have been found to cross the placenta; paroxetine and sertraline pass through the placenta more slowly than fluoxetine.[29] During the first trimester, the main concern is malformation of the fetus, although there is no robust evidence that SSRIs or venlafaxine cause increased teratogenicity. Concerns in the third trimester focus on neonatal withdrawal because third trimester exposure to ADs has been correlated with a higher risk of adverse effects such as respiratory distress, feeding difficulties, and LBW.

One systematic review and metaanalysis[30] included 9 prospective observational studies (retrospective design studies were excluded) that described late pregnancy exposure (at least third trimester exposure) to any SSRI, focusing on the incidence of prematurity, LBW, admission to an SCN or NICU, and the diagnosis of poor neonatal adaptation. This study found that neonates exposed to SSRIs in utero are more likely to have LBW and to be admitted to an SCN or NICU at birth. However, these effects have been shown to be transient, and there is some heterogeneity between the exposed populations of the included studies. The findings of the Lattimore review[30] are in contrast with the findings of one prospective, multicentre, controlled cohort study.[31] This study aimed to assess the safety and risk to the fetus of some SSRIs (specifically, fluvoxamine, paroxetine, and sertraline) in terms of rates of major congenital malformations. In total of 267 women exposed to an SSRI and 267 control subjects, the SSRIs did not appear to increase the teratogenic risk when used in their recommended dosages. These results are confirmed by a recent systematic review, which found that the newer ADs, as a group, are not associated with an increased risk of major malformations above the baseline of 1% to 3% in the population.[32] However, regulatory agencies have issued some warnings about the risk that neonates exposed late in the third trimester to SSRIs (especially paroxetine) or SNRIs may develop complications requiring prolonged hospitalization, respiratory support, and tube feeding.[33] Further, the US FDA has determined that exposure to paroxetine in the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiac malformations.[34] At the FDA's request, the manufacturer has changed paroxetine's pregnancy category from C to D and added new data and recommendations to the warnings section of paroxetine's prescribing information. The FDA is awaiting the final results of the recent studies and accruing additional data related to the use of paroxetine in pregnancy to better characterize the risk for congenital malformations associated with this drug.

Confounding by other risk factors needs to be considered in these observational studies. Many studies included the following in the SSRI-exposed group: women taking other psychotropic medications (that is, benzodiazepines), women using SSRIs for indications other than depression (for example, anxiety), or women who smoked cigarettes and used alcohol.[35,36] Cigarette smoking is known to adversely affect infant growth in utero, and alcohol abuse has been associated with prematurity and small-for-gestational age infants.[30] In addition, almost all the included studies compared SSRI-exposed women with healthy control populations having no psychiatric diagnosis, even though the proper comparisons would have been between women diagnosed with major depressive disorder who were receiving SSRIs and women with major depressive disorder who were not receiving pharmacotherapy. The perinatal period can become a critical time to screen for and identify depression because pregnant women have increased contact with health services. Given the potential impact of antenatal mental disturbances on maternal and infant outcomes, pregnant women can require psychiatric evaluation.[37] If women with clinically significant depression refuse treatment during pregnancy, possible adverse outcomes such as suicidal tendencies, deteriorating social functions, psychosis, and inability to comply with obstetrical evaluations should be closely monitored and assessed.[38]

Considering that maternal depression during pregnancy has been associated with premature delivery and LBW[39–41] and that every mother and baby metabolize medication differently, no generally applicable statement can be made about the choice of a particular medication during pregnancy. When a woman is treated with ADs during pregnancy, her physician should clearly inform her about the risk of teratogenesis, neonatal toxicity, and possible long-term effects on child development.[42–44] This is an area that requires much more research. However, a woman who is pregnant or planning a pregnancy and currently taking an AD should consult with her physician about whether to continue taking it. It is important not to stop taking the drug without discussing the best way to do that with one's physician.

Infant Exposure to Maternal SSRI Therapy During Breast-Feeding

There is no clear way to estimate neonatal drug exposure through lactation by monitoring maternal or breast-milk drug levels, and the clinical significance of low infant drug levels remains unclear. Adverse effects from breast-feeding exposure have been mainly documented in case reports. The most commonly reported infant signs are uneasy sleep or irritability and poor feeding or sucking. The long-term effects on newborns after chronic low-dosage AD exposure through lactation has not been well studied, and information is limited.[45,46]

One pooled analysis of 57 published and unpublished studies looking at AD levels in lactating women, in breast milk, and in nursing infants found that drug levels in maternal breast milk were significantly correlated with infant plasma levels of citalopram, fluoxetine, and paroxetine.[47] It has also been found that infants exposed to venlafaxine had high serum levels of this AD and its metabolite, even though there was no increase in adverse symptoms in drug-exposed infants compared with a nonexposed group.[48] Several studies have sought to establish the peak drug concentration in breast milk after maternal dosing as a strategy to minimize infant exposure.

The benefit of breast milk to infants has been well established[49]; by contrast, the possible harm of an untreated maternal mood disorder on the mother–infant relationship and on baby development should also be considered. Better-controlled studies of short-term and long-term infant outcomes are needed. Meanwhile, decisions about lactation involve careful risk–benefit analysis and should be assessed on an individual basis by the patient and her physician, and should also include the other members of the family.

ADs and Suicide

Current evidence indicates no clear causal relation between SSRIs and increased risk for suicide in adults, but SSRIs may induce or worsen suicidal ideation and behaviour during the early phases of treatment (see Note), possibly owing to increased agitation and activation.[50] Two systematic reviews analyzed suicidal ideas and completed suicides in randomized trials of AD drugs. Fergusson and colleagues conducted a systematic review of published RCTs comparing SSRIs with either placebo or other active treatments in patients with depression and other clinical conditions.[51] They found an almost twofold increase in the odds of fatal and nonfatal suicidal attempts among SSRI users when they were compared with users of placebo or other therapeutic interventions (excluding TCAs). However, in the case of fatal suicidal attempts only, no increase in risk was observed among those taking SSRIs, compared with those taking placebo. Finally, when overall suicide attempts were compared, no differences were observed between those taking SSRIs and those taking TCAs. By contrast, Gunnell and colleagues[52] included in their review both published and unpublished RCTs that pharmaceutical companies had submitted to the safety review of the MHRA. These trials compared SSRIs with placebo in adults with depression and other clinical conditions. Three outcome measures were studied: completed suicide, nonfatal self-harm, and suicidal thoughts. No evidence for an increased risk of completed suicide was found; further, their analysis found only weak evidence for an increased risk of self-harm and inconclusive evidence of an increased risk for suicidal thoughts (estimates compatible with a modest protective or adverse effect).

From a methodological point of view, the following important limitations should be taken into account: short follow-up, nonspecific study design to identify completed or attempted suicides specifically, selective reporting of outcome, and inclusion of different populations in terms of diagnosis. Although this randomized evidence is supported by observational data,[53–56] important concerns have recently been raised about the transparency of the information available in RCTs regarding the link between ADs and suicide risk.[57] However, some useful insights can be drawn for clinical practice.[50,58] First of all, current evidence indicates no clear causal relation between SSRIs and suicide, and robust evidence is available for the efficacy of treatment with ADs in the pharmacologic management of moderate-to-severe unipolar depression. This should encourage doctors to prescribe effective dosages of these drugs in patients with moderate-to-severe depression.

It should be emphasized that these indications apply to adults only. In children and adolescents, the balance between benefits and harms seems to be negative, with little evidence for efficacy and increasing evidence for an association between exposure to SSRIs and other ADs and the emergence of suicidal thought and behaviours.[59,60] Therefore, the routine prescribing of ADs for children and adolescents should be discouraged.

Conclusions

Residual Uncertainty

This review focused on selected clinical issues; however, many other issues are of crucial importance for daily clinical practice. This selective reporting is the result of our subjective choice of what we considered most important, but it is also due to the absence of good evidence in regard to some clinical questions. This does not diminish the importance of several of these questions, for example, the question of the possible association between treatment with SSRIs and the increased risk of bleeding events. Numerous case reports, population-based cohort studies, and national registry analyses have reported the occurrence of such problems.[61] That said, no reliable epidemiologic data exist with regard to the incidence of

bleeding events in patients treated with SSRIs, nor have clinical trials been sufficiently powered to address this issue.[62] The types of bleeding complications associated with SSRIs support the platelet deficiency in their origin; concomitant use of other drugs (that is, nonsteroidal antiinflammatory drugs, angiotensin receptor blockers, and long-term antiplatelet regimens) can also contribute to the increase in bleeding events. Bleeding complications are considered to be rare, although their frequency is growing. Many events have been reported for earlier SSRIs, such as fluoxetine, because they have been studied for longer and patients have had longer exposure to them. Correspondingly, reports of bleeding complications with novel medications such as escitalopram are still rare, and more evidence is need for compounds such as venlafaxine or trazodone, which exhibit partial SSRI activity. Thus the essential clinical message is to be aware of potential SSRI-induced hemorrhages, especially in patients with even mild hereditary platelet defects and in patients treated with antiplatelet agents. Similarly, some evidence points to a suggested higher risk of cerebrovascular adverse reactions for SSRI users.[63]

With regard to methodological considerations, a main problem is the evidence of publication bias in AD trials (especially regarding SSRIs). Most drug trials are conducted or supported by the pharmaceutical industry, and sponsorship may influence the assessment of study outcomes. From unpublished trials to individual patient data, the lack of access to primary data prevents the integration of study results to produce meaningful findings. Given their importance, it is urgent that all trial data be accessible to independent organizations involved in synthesizing research.

Most RCTs included in systematic reviews were short-term and focused exclusively on improvement in depressive symptoms. Longer-term RCTs that could provide more data on the sustainability of benefits, as well as on potential adverse effects, are lacking but strongly needed. Most RCTs analyzed results according to the last observation carried forward—a method that could bias the estimate of treatment efficacy. A "pure" intention-to-treat analysis that follows participants for the whole trial duration, even if they withdraw, would be more conservative and would replicate what happens in clinical practice. Although the effects on depressive symptoms are clear, effects on functional status and health-related quality of life outcomes are usually not reported. The safety of AD drugs is currently under review by regulatory authorities in several countries, and in light of this, practitioners should be guided by the recommendations and warnings issued by their national drug regulatory authorities with respect to the prescribing of ADs.

Note

Regulatory authorities in Europe, the United Kingdom, and the United States have issued warnings about the use of SSRIs in children and adolescents. The European Medicines Agency has ruled that SSRIs and SNRIs should not be prescribed for depression in children and adolescents under age 18 years. The UK Committee for the Safety of Medicines has advised that the balance of risks and benefits for the treatment of depression in the pediatric population is unfavourable for paroxetine, citalopram, sertraline, venlafaxine, escitalopram, and mirtazapine. The regulatory authority in the United States requires a safety warning in bold text about suicide risk in package inserts for all ADs.

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Résumé : Méta-examen de l'efficacité à court terme et de l'innocuité des antidépresseurs pour la dépression : une approche fondée sur des données probantes pour éclairer la pratique clinique

Objectif : Examiner la documentation scientifique disponible pour trouver des réponses à des questions cliniquement pertinentes au sujet de l'efficacité et de la tolérabilité des antidépresseurs (AD) pour le traitement de la phase aiguë de la dépression et pour évaluer le degré auquel la documentation appuie les résultats.

Méthodes : Nous avons utilisé plusieurs sources pour repérer les principales études. Nous avons cherché dans MEDLINE, EMBASE, PsycINFO et *Cochrane Library* jusqu'à avril 2006. Des recherches additionnelles ont été menées dans les bases de données britanniques suivantes : *National Health Service Centre for Reviews and Dissemination: Abstracts of Reviews of Effects, Health Technology Assessment*; et *Turning Research into Practice*. En outre, nous avons recherché le site Web *National Institute of Health and Clinical Excellence guidance*. Nous avons mené un méta-examen d'études systématiques choisies de qualité supérieure sur les interventions pharmacologiques à court terme utilisant des AD pour la dépression majeure. Pour évaluer l'efficacité, nous avons suivi la hiérarchie des données probantes proposée par le centre de médecine fondée sur des données probantes (Oxford), incluant seulement les études d'essais contrôlés randomisés. Pour évaluer la tolérabilité, nous avons aussi pris en compte les données observationnelles, en l'absence de données probantes randomisées.

Résultats : Il y avait des données probantes randomisées confirmant que les AD sont efficaces dans le cadre des soins primaires et qu'il peut y avoir des différences légères, mais importantes sur le plan clinique, entre les AD. Aucunes données probantes solides ne confirmaient qu'un AD combiné avec un antipsychotique est supérieur à une monothérapie d'AD dans les cas de dépression psychotique ou que l'administration intraveineuse entraîne une réponse plus rapide. Il y avait des données probantes à l'effet que les inhibiteurs de la monoamine oxydase sont supérieurs aux antidépresseurs tricycliques, mais pas aux inhibiteurs spécifiques du recaptage de la sérotonine (ISRS) pour traiter la dépression atypique. Certaines données probantes soutiennent les dommages liés à l'utilisation des ISRS durant la grossesse, mais pas pendant l'allaitement. Des données probantes confirment que les ISRS peuvent accroître les idées suicidaires, mais pas le suicide même, dans les premières phases de la thérapie.

Conclusions : Nous avons trouvé un ensemble substantiel de données probantes sur les avantages et les effets nuisibles des AD dans le traitement du trouble dépressif. Néanmoins, il demeure une quantité considérable d'incertitude résiduelle. Les données probantes sont inadéquates pour des recommandations d'application générale; dans la plupart des cas, l'équilibre entre les risques et les avantages devra être pris en compte pour les patients individuels. Les cliniciens devraient aussi se laisser guider par les recommandations et les avertissements émis par les organismes de réglementation des médicaments.