Pharmacological and Combined Interventions for the Acute Depressive Episode: Focus on Efficacy and Tolerability

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REVIEW

Pharmacological and combined interventions for the acute depressive episode: focus on efficacy and tolerability

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Background: Use of antidepressants is the gold standard therapy for major depression. However, despite the large number of commercially available antidepressant drugs there are several differences among them in efficacy, tolerability, and cost-effectiveness. In addition the optimal augmentation strategy is still not clear when dealing with treatment-resistant depression, a condition that affects 15% to 40% of depressed patients.

Methods: We therefore reviewed the main characteristics of these drugs regarding their efficacy, tolerability, side effects and cost-effectiveness, by accessing all meta-analyses and systematic reviews published from 2004 to 2009. In addition, we reviewed the augmentation strategy of associated antidepressants with neurostimulation therapies (such as transcranial magnetic stimulation [TMS] and transcranial direct current stimulation [tDCS]). A search was undertaken in MEDLINE, Web of Science, Cochrane, and Scielo databases. We included: 21 meta-analyses of antidepressant trials, 15 neurostimulation clinical trials and 8 studies of pharmacoeconomics. We then performed a comprehensive review on these articles.

Results and Conclusion: Although recent meta-analyses suggest sertraline and escitalopram might have increased efficacy/tolerability, other studies and large pragmatic trials have not found these to be superior to other antidepressant drugs. Also, we did not identify any superior drug in terms of cost-effectiveness due to the different designs observed among pharmacoecomics studies. Side effects such as sexual dysfunction, gastrointestinal problems and weight gain were common causes of discontinuation. Tolerability was an important issue for novel neurostimulation interventions, such as TMS and tDCS. These therapies might be interesting augmentation strategies, considering their benign profile of side effects, if proper safety parameters are adopted.

Keywords: acute depressive episode, pharmacological interventions, combined interventions

Introduction

The use of pharmacotherapy in psychiatry started in the beginning of the 19th century with the introduction of morphine, lithium, potassium bromide, and chloral hydrate for the treatment of some mental conditions.[1] However, "modern" psychopharmacology – as a field linking the advances in neuropharmacology, psychiatric nosology and clinical research[2] – dates from the late 1950s, when drugs such as chlorpromazine, haloperidol, reserpine, and imipramine started to be used in hospitalized patients and, later on, in other psychiatric settings.[3] Since then numerous psychopharmacological drugs have been developed and introduced into clinical practise. The intensive development of psychopharmacology has resulted in the development of different agents that may be divided into four major classes of antidepressant drugs: tricyclic antidepressants (TCAs); monoamine oxidase inhibitors (MAOIs); selective serotonin reuptake

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inhibitors (SSRIs); and serotonin-norepinephrine reuptake inhibitors (SNRIs) in addition to a variety of other miscellaneous antidepressant drugs[4,5] (Table 1).

The large number of available antidepressants is not only a result of market forces, but also a result of varied efficacy, differential pricing, and especially adverse effects of the different available drugs. For example, although older (TCAs, MAOIs) and newer (SSRIs, SNRIs) antidepressants might not differ substantially in efficacy,[6,7] the use of older antidepressants have generally decreased because they are associated with increased side effects and toxicity.[8] Even for newer antidepressants, there are important differences in side effects across the range of available drugs. Additonally more intense side effects are associated with higher dropout rates.[9] A similar issue is observed for efficacy as there is still no consensus on which are the most effective antidepressant drugs, for example, while one meta-analysis suggests that newer SNRIs have greater efficacy than SSRIs,[10] other studies suggest that mirtazapine and milnacipran have similar efficacy to modern SSRIs.[11,12] Studies from the 1980s showed MAOIs to have greater efficacy than TCAs for treatment-resistant depression.[13,14] Here the study population is an important factor in explaining these differences.

Another critical issue when making comparisons across antidepressants is the methodological issues involved in clinical trials that can affect the interpretation of results such as:

a) The placebo response of MDD clinical trials is very high[15,16] which might lead to a ceiling effect to the truly antidepressant response;[17]
b) Placebo response has also grown through time, thereby favoring new trials to fail;[18,19]
c) Differences in trial design when comparing against placebo or against active drug modify drug response;[20]
d) Major depression, being a heterogeneous construct of disease,[17] increases group variance, decreasing internal validity and leading results towards the null hypothesis, and;
e) Head-to-head comparisons are often designed as noninferiority studies – ie, studies testing the hypothesis that one drug does not "significantly differ" from others – since the cut-off point of significance (ie, the difference that is acceptable when considering there is no clinical difference) in such studies is quite arbitrary. Therefore it is difficult to draw valid conclusions regarding the efficacy, tolerability and cost-effectiveness of such drugs.

Besides the differences in efficacy and side effects, the other main issue is when treatments with antidepressants fail. In this case, several strategies have been proposed, such as dose uptitration, switching, or combining antidepressants, psychotherapy, and augmentation with nonantidepressant drugs.[21] However, the use of multiple medications also increases the risk of side effects, drug–drug interactions, and overall costs of treatment. Additionally, it is unclear how long the add-on treatment should be maintained, if at all, after the remission of depression as this can prolong its use beyond necessary.[22,23]

An alternative is to combine antidepressants with neurostimulation therapies as augmentation strategies, such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and transcranial direct current stimulation (tDCS)[24] to hasten remission. For example, a recent sham-controlled trial showed that active rTMS hastened the effects of venlafaxine, escitalopram and sertraline.[25] Moreover, an ECT meta-analysis revealed its efficacy in treating acute depression when combined to antidepressants.[26] Neurostimulation techniques have been increasingly studied in the past decades as an augmentation alternative for treatment-resistant depression.[27] However, the benign profile of adverse events and invasiveness of newer techniques such as tDCS and rTMS has also stimulated clinical trials in less refractory patients.

Table 1 Summary of antidepressant classes and common brands

MAOIs	SSRIs	SNRIs	TCAs	Others
Tranylcypromine	Fluoxetine	Venlafaxine	Amitriptyline	Bupropion
Phenelzine	Paroxetine	Duloxetine	Clomipramine	Mirtazapine
Isocarboxazid	Sertraline	Milnacipran	Imipramine	Reboxetine
Transdermal selegine	Fluvoxamine	Desvenlafaxine	Nortriptyline	Trazodone
	Citalopram			Nefazodone
	Escitalopram			

Abbreviations: TCAs, tricyclic antidepressants; MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin-norepinephrine reuptake inhibitors.

Repetitive transcranial magnetic stimulation is being increasingly studied in neuropsychiatric disorders as it generates a strong magnetic field that induces an electric current within the brain in order to modulate a specific cortical brain area.[28] Recently, rTMS has been approved in the US for treatment of patients with major depression who have not responded to a single antidepressant drug trial.[29] Additionally rTMS has also been approved for clinical use in other countries such as Canada, Italy, Israel, and Brazil. Transcranial direct current stimulation induces a weak direct current in the cortex, and depending on the duration and polarity of stimulation, it can induce an increase or decrease of cortical excitability.[30] Initial tDCS studies show promising results in recent clinical trials for major depression.[31]

The aim this comprehensive review is therefore two-fold:

a) To summarize the main aspects (efficacy, safety, tolerability) the physician should consider when choosing an antidepressant for the acute depressive episode;
b) To review the use of neurostimulation treatments as nonpharmacological alternatives for augmentation strategies with antidepressants for the acute depressive episode.

Finally, it should be underscored that in this review we use the accepted definitions standard applied in clinical research, ie, the acute phase usually lasts 6 to 8 weeks and ends with remission of symptoms, (usually indexed as a Hamilton Depressive Rating Scale < 8), thus indicating a pre-morbid levels of function. Response is defined as the reduction of the depressive symptoms (usually indexed in more than 50% of the baseline scores of a depressive mood scale). The continuation phase lasts 4 to 9 months, in which treatment is continued to prevent re-emergence of symptoms (relapse), followed by the maintenance phase that lasts indefinitely, or until the patient presents a new depressive episode (recurrence).[32]

Methods

Literature search

We searched for articles published in the last 5 years (2004 to May 2009, including online articles published "ahead of print") in the following databases: MEDLINE, Web of Science, Cochrane, and Scielo. We used the following keywords: "meta-analysis" or "systematic review"; "antidepressant drugs"; and "major depression" or "depression" or "major depressive disorder". We also performed additional searches with the keywords: "transcranial magnetic stimulation" or "direct current stimulation" or "ECT" and "antidepressants" to assess the efficacy of neurostimulation augmentation strategies.

Selection criteria for antidepressants: We chose to analyze meta-analysis studies and systematic reviews instead of individual clinical trials because:

a) Several meta-analyses of efficacy and tolerability have already been performed in this short period of time, thus we chose to review these meta-analyses rather than performing another meta-analysis on the topic and generating redundant data;[33–35]
b) Since the goal of this paper is to provide an overview of efficacy and acceptability of antidepressants, we chose to identify the articles summarizing the evidence found in clinical trials, thus prioritizing a comprehensive review of such evidence.

Focusing on meta-analyses allowed us to restrict our publication search time period to the last 5 years, as meta-analyses are able to assess the evidence of prior trials. The eligibility criteria were:

a) Manuscripts written in English;
b) For efficacy studies – meta-analyses that compared several antidepressant drugs (we did not include meta-analyses of an specific drug);

Table 2 Summary of meta-analyses that compared antidepressants vs placebo

Author	Antidepressant	Condition	Studies (subjects)	Main results	Comments
Chen[41]	All	PSD	16 (1320)	ES = 0.23 for AD (response)	Longer treatments might be more effective
Nelson[40]	2nd gen	Geriatric	10 (4165)	ORs = 1.4 vs placebo (remission)	Significant heterogeneity of outcomes
Arroll[43]	All	Prim. care	15 (2753)	NNT = 4–6 vs placebo (remission)	Both TCA and SSRI were effective
Kirsch[42]	2nd gen (4 AD)	Adult	35 (5133)	d = 0.32 (mood score)	Included unpublished studies

Abbreviations: OR, odds ratio; RR, relative risk; ES, effect size; AD, antidepressants; NNT, number needed to treat; d, Cohen's *d* (a measure of effect size); TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors PSD, post-stroke depression.

c) For safety studies – meta-analyses of adverse effects, incidence of suicide and tolerability;
d) Other meta-analyses on pharmacoeconomics and cost-effectiveness.

The selection criteria for neurostimulation interventions were controlled trials in which a non-pharmacological was combined with a pharmacological therapy – ie, an (active device + drug) vs (sham device + drug) trial. Eligibility criteria were:

a) Manuscripts written in English;
b) Efficacy and safety studies: double-blinded, sham-controlled, randomized trials;
c) Cost-effectiveness: pharmacoeconomics analysis.

Finally, other neurostimulation techniques, such as deep brain stimulation (DBS) and vagus nerve stimulation (VNS) are not covered in this study because they are invasive surgical techniques associated with an increased risk of adverse effects. More specifically the purpose of our review is to assess neurostimulation strategies that can be more straightforwardly applied during an acute depressive episode.

Results

For antidepressant drugs

Using the keywords and time limits defined above, we were able to find 111 records in MEDLINE. Of these, 90 references were excluded because

a) Other articles formats (letters to the editor, clinical trials, comments, qualitative reviews);
b) Meta-analyses focusing on one specific antidepressant drug, nonantidepressant drugs, or other methodological approaches.

Therefore, 21 articles were reviewed.

For neurostimulation interventions

There were 123 rTMS records found and those deemed unsuitable were excluded for similar reasons to those above. Thirteen articles were reviewed for efficacy and 1 for pharmacoeconomics analysis.

For tDCS, 25 records were found though only 4 clinical studies were initially included. However, 3 of these,[36–38] used medication-free patients and the remaining one was open label.[39] No pharmacoeconomics analyses were identified for this group.

For ECT, of 36 records found 33 were excluded, (open-label, naturalistic, retrospective studies), leaving 1 clinical trial and 2 pharmacoeconomics studies that were included.

Efficacy of new-generation antidepressants in prophylaxis, maintenance and treatment-resistant depression

We identified 9 studies focusing on the acute-term efficacy of antidepressants. Four meta-analyses were performed: 1 in late-life depression[40] 1 in post-stroke depression,[41] and 2 in adult patients.[42,43] All these compared the the difference in drug–placebo response at end-of-treatment, which was between 4 and 8 weeks.

The meta-analysis on post-stroke depression[41] assessed 16 randomized clinical trials and showed that depression response was superior in patients using antidepressants (65%) when compared to those using placebo (44%), 12 of the 16 studies used SSRIs. Subgroup analyses showed a significant time effect in antidepressant group, ie, increased duration of treatment response and remission rates. A second meta-analysis focused on second-generation antidepressants in late-life depression.[40] Ten randomized clinical trials were analyzed which indicated that antidepressants are significantly superior to placebo regarding response (odds ratio [OR] = 1.4, 95% confidence interval [CI] = 1.24–1.57) and remission (OR = 1.22, 95% CI = 1.05–1.42) rates. There was also a time effect identified in the antidepressant group.

Two meta-analyses compared antidepressants vs placebo in adult patients. In 2005, a meta-analysis of depression in primary care[43] analyzed 15 studies (3 on SSRIs) showing response rates from 56% to 60% for antidepressants vs 42% to 47% for placebo. However, most trials were of low methodological quality. A further meta-analysis published

Table 3 Summary of meta-analyses that compared antidepressants vs "new" antidepressants

Author	Antidepressant	Studies (number of patients)	Main results	Comments
Hansen[44]	"New" AD	46 (N/A)	No difference in AD efficacy	Quantitative analyses were not done
Montgomery[45]	6 AD	N/A (N/A)	ESC probably superior	Not a systematic review
Cipriani[33]	2nd gen (12 AD)	117 (25928)	ESC and SERT superior	Direct/indirect comparisons

Notes: "New" AD refers to new antidepressants, such as selective serotonin reuptake inhibitors (SSRI).
Abbreviations: ESC, escitalopram; SERT, sertraline.

in 2008[15] reviewed 35 published and unpublished trials comparing seven new-generation antidepressant drugs against placebo. The authors concluded that although a statistical difference for mean drug–placebo response was obtained (1.8 on Hamilton Depression Rating Scale), it did not reach the 3-point difference that translates into clinical significance. Moreover, meta-regression analysis showed that antidepressant drugs only achieved clinical significance when baseline severity scores were high (corresponding to severe depression).

Three meta-analyses involved drug-drug trials that perform direct and indirect comparisons for efficacy, safety and other outcomes. Hansen and colleagues[44] assessed and reviewed 46 head-to-head trials comparing one new-generation antidepressant to another, concluding "second-generation antidepressants probably do not differ substantially for treatment of major depressive disorder". However, only direct comparisons (meaning results from a head-to-head clinical trials) were performed, which might limit the generality of the results as only few comparisons could be made. The meta-analysis of Montgomery et al[45] also performed direct head-to-head comparisons, concluding that "only a very few antidepressants are shown to be more effective than others", while pointing out for a "possible superiority" for milnacipran and clomipramine, a "probable superiority" for venlafaxine, and a "definite superiority" for escitalopram. However, only direct comparisons were performed and these too might limit the generality of both meta-analyses. Finally, Cipriani et al[33] performed a meta-analysis comparing 12 new-generation antidepressants (buproprion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine) for efficacy and acceptability by reviewing 117 controlled trials and performing direct and indirect comparisons. The authors' conclusion was that the antidepressants mirtazapine, escitalopram, venlafaxine, and sertraline were significantly more effective than the others, and that escitalopram and sertraline showed the best profile of acceptability.

Efficacy of new-generation antidepressants for major depression in other contexts (prophylaxis, prevention of relapse and recurrence, treatment-resistant depression).

We identified 4 meta-analyses on the above topic.[46–49] Two meta-analyses focused on treatment discontinuation and risk of relapse. One of these[46] reviewed 5 clinical trials in which 1009 patients were chosen at random to receive a full antidepressant dose or a reduced dose (generally half of antidepressant dose). After 8 to 12 weeks, the relative risk of relapse using lower doses compared to the full dose, was 1.62 (95% CI = 1.23–2.15). The other meta-analysis[48] focused on comparing by antidepressant class (SSRI vs TCA) and the degree of refractoriness (single major depression episode vs recurrent depression). Thirty trials, enrolling 4890 patients, were reviewed. Results showed that the use of antidepressants, regardless of their class, reduces relapse risk over 1 year of follow up (OR = 0.24 for SSRI, OR = 0.29 for TCI). Patients with recurrent depression have an increased risk of relapse than those with a single major depression episode. One meta-analysis[47] looked for evidence of antidepressant prophylaxis for post-stroke depression. In reviewing 10 clinical trials in which this intervention was performed in nondepressed patients after a stroke. The pooled analysis showed that the occurrence rate of depression in patients using antidepressant was 12.5%, against a significant difference of 29.17% in patients in control group, which suggests the use antidepressants in non-depressed patients after a stroke might be worthwhile. The meta-analysis study of Hansen et al[49] reviewed evidence of the efficacy of new-generation antidepressants in preventing major depression relapse involving four head-to-head trials and 23 placebo-controlled trials. The study found that although no differences were observed in comparative trials, in placebo trials the NNT is 5 (95% CI 4–6) for preventing relapse and recurrence of major depression episodes.

New-generation antidepressants – side effects and tolerability

Seven meta-analyses reviewed the safety, tolerability, and some side effects related to antidepressant use.[33,44,50–54] One meta-analysis[51] reviewed specifically the safety of using antidepressants in breast-feeding women by analyzing studies that measured maternal and infant plasma levels, together with breast milk levels. Fifty-seven studies were included which tested amitryptiline, clomipramine, dothiepin, imipramine, buproprione, citalopram, fluvoxamine, fluxoetine, nortriptlyine, sertraline, and nefazodone. The conclusion was that nortriptyline, paroxetine, and sertraline might be the preferred choices in these patients, while citalopram dosage should be reduced as this drug produced elevated plasma levels in 17% of infants. The meta-analysis understaken by McIntyre et al[50] reviewed antidepressant effects on lipid metabolism and found that drugs related to weight gain (tryciclics, mirtazapine) are more likely to induce changes in lipid profile than weight neutral drugs (buproprion, venlafaxine, duloxetine). However, the meta-analysis was unable to assess whether or not there is a weight-independent effect related to some antidepressants. The more recent meta-analysis of Serretti et al[54] demonstrated that the risks and rates of sexual dysfunction were highest in the antidepressants sertraline, citalopram, fluoxetine, paroxetine, and venlafaxine followed

by fluovoxamine, escitalopram, duloxetine, phenelzine, and imipramine, while agomelatine, mirtazapine, bupropion, amineptine, and nefazodone showed rates similar or inferior to placebo.

Four other meta-analyses focused on the general harms and safety of new-generation antidepressants. Hanset et al[44] found that venlafaxine produced significantly more nausea/vomiting and dizziness than the other antidepressants, with a mean incidence of 31% and 16%, respectively. One study suggested that this drug was also associated with increased blood pressure, while bupropion users showed an increased incidence of headache (27%) and insomnia (16%). Other important side effects, such as weight gain and sexual side effects, were not addressed because of inadequate reporting and great variability in assessment methods. Gartlehner and colleagues performed 2 meta-analyses[52,53] including 203 and 104 studies and found that: venlafaxine had the highest rates of discontinuation, probably because of increased incidence of nausea and vomiting, while sertraline had the highest incidence of diarrhea, mirtazapine and paroxetine were associated with greater weight gain, and trazodone with increased somnolence. For sexual dysfunction rates, buproprion presented significantly less, while paroxetine presented significantly more, compared to other second-generation antidepressants. Finally, Cipriani et al[33] aimed to rank 12 new-generation antidepressants for their efficacy and tolerability (measured by dropout rate) with data extracted from 117 trials and observed that escitalopram and sertraline were tolerated significantly more than venlafaxine and other SSRIs, Both these drugs showed the potential for being first-line treatment as they showed increased efficacy over venlafaxine and other SSRIs. In addition sertraline demonstrably had the most favorable balance between benefits, acceptability, and acquisition costs.

Finally, we identified no meta-analyses focusing on antidepressants compliance (ie, treatment adherence in clinical practice that is influenced by a combination of side effects, tolerability, individual characteristics, patient–physician relationship and treatment costs), therefore it is still not clear whether or not antidepressant drugs differ in compliance.

Safety of new-generation antidepressants – the risk and rates of suicide

The meta-analysis study of Hammad et al[55] assessed individual patient data from 207 trials, for a total of 40,028 patients with major depression. They identified 21 cases of suicide. In placebo-controlled trials there were 5 suicides (1.5/1000 person-years), while in active-only trials there were 16 suicides (11.1/1000 person-years). Although Poisson regression analysis indicated this was not a significant difference the authors concluded that with such a small number of suicides any increased suicide risk in patients taking antidepressant drugs cannot be definitively excluded.

Studies of pharmacoeconomics and cost-effectiveness

Five meta-analyses were included,[56–60] focusing on the pharmacoeconomics of escitalopram, sertraline and the budget-impact of SSRIs, SNRIs, and TCA in Brazil, Colombia, the UK, and worldwide. In 2004, a cost-effectiveness analysis of escitalopram compared the drug against other SSRIs and venlafaxine, concluding that escitalopram costs were systematically lower than the other drugs.[60] Another analysis performed in the same year compared the cost of SNRI vs SSRIs vs TCA in the UK. This suggested that venlafaxine might be a cost-effective first-line drug compared with the SSRIs and TCAs.[59] In 2005, a cost-effectiveness review enrolled several studies performed in nine countries comparing SNRIs vs TCAs vs SSRIs and concluded that the higher initial cost of SNRI is probably compensated by higher success rates of drugs of this class.[58] In 2007, a budget-impact analysis to evaluate the impact of SNRI introduction in the Brazilian national drug-free formulary used an existing decision-tree analysis and concluded that, from a public healthcare perspective, there are no significant difference in cost-effectiveness between the drug classes of SNRIs, SSRIs, and TCAs.[56] The same authors performed another budget-impact analysis to evaluate the cost-effectiveness of amitriptyline, fluoxetine and venlafaxine in Colombia and found that amitriptyline was more cost-effective compared to the other two drugs (venlafaxine costs were evaluated for the brand-name product, as generics were not currently available in that country).[57]

Neurostimulation augmentations strategies for the acute depressive disorder

Electroconvulsive therapy (ECT)

Sackeim et al[61] performed a multi-center trial that enrolled 319 patients with treatment-resistant, severe depression in a 2×3 factorial design trial (patients received either unilateral or bilateral ECT vs nortriptyline or venlafaxine or placebo). Although all groups were effective, post-hoc analysis showed the association of nortriptyline with ECT to be superior of

placebo with ECT (the group venlafaxine with ECT did not differ from others).

Two studies assessed the pharmacoeconomics of ECT. Greenhalgh et al[62] reviewed the evidence of clinical and cost-effectiveness of ECT for depressive illness, schizophrenia, catatonia, and mania. For major depression, they concluded ECT to be probably more effective than pharmacotherapy in the short term; that TCAs might improve ECT effects during the treatment; and that there is limited evidence of long-term efficacy of ECT and the impact of ECT on suicide and all-cause mortality. They concluded that there is still much uncertainty whether ECT is a cost-effective treatment. McLoughlin et al[63] performed a pragmatic randomized trial to compare rTMS vs ECT with 6-month follow-up, evaluating depression improvement and gains in quality-adjusted life-years (QALYs). They concluded that ECT was superior to rTMS at end-of-treatment (3 weeks) but not at follow-up (6 months). Also, the overall treatment costs of both therapies were similar as well as QALYs improvement.

Transcranial direct current stimulation (tDCS)

The trial of Loo et al[64] enrolled 40 depressed patients that had already failed 1 antidepressant trial to receive either active or sham tDCS (5 sessions, 1 mA, anodal on the left). Their study failed to prove any significant differences between active and sham treatment groups.

Repetitive transcranial magnetic stimulation (rTMS)

Nine studies tested the efficacy of rTMS as an augmentation strategy,[65–73] ie, patients already on antidepressant drugs (mostly with treatment-resistant depression) that used rTMS to ameliorate of symptoms. In 2005, Su et al[65] tested the efficacy of 2-week fast rTMS in 30 treatment-resistant depression patients and found a statistically significant superior response rate in the active group (60% vs 10%). Rossini et al[66] in the same year, with similar design (2-week fast rTMS in treatment-resistant depression), enrolled 50 patients. Two parameters of stimulation were tested (80% vs 100% intensity of motor threshold [MT]). The response rates were 61%, 27%, and 6.2% in 100% MT, 80% MT, and sham; the 80% MT group did not differ from the placebo group.

In 2006, Avery et al[67] tested in 68 treatment-resistant depression patients with real (3-week, fast rTMS) or sham rTMS. They found superior response and remission rates in the active group (30.6% vs 6.1%, $P < 0.01$; 20% vs 3%, $P < 0.3$, respectively). Fitzgerald et al[68] conducted a 6-week trial in 50 patients with treatment-resistant depression, combining bilateral stimulation in the active group against a sham group. They demonstrated there was greater response and remission rates in the active groups (44% vs 8% and 36% vs zero, respectively). Garcia-Toro et al[69] compared bilateral stimulation with SPECT-targeted stimulation and a sham group. In a sample of 30 patients they found both active treatments to be superior (improvement of 23% vs 32% vs 5%, respectively). In 2007, Anderson et al[70] tested the efficacy of fast rTMS 3 times a week in a sample of 29 treatment-resistant patients and found response rates of 55% in the active sample and 7% in the placebo group ($P < 0.05$). In a small trial, Bortolomasi et al[71] tested the efficacy of fast rTMS vs sham in 19 patients. They also found superior improvement in the active group. Loo et al[72] tested the efficacy and safety of twice-daily rTMS over 2 weeks in 38 treatment-resistant depression patients, observing a greater improvement in the active patients than in the sham group at end-of-treatment (2-week) and follow-up (6-week). Finally, Mogg et al[73] studied the effects of long-term (4-month) treatment of rTMS, randomizing 59 patients to receive either 10 sessions of fast rTMS or sham; however there was no significant difference between groups for any time period.

We identified 4 articles that used rTMS as an accelerating strategy (ie, when both interventions were tested simultaneously to hasten antidepressant efficacy) for patients with treatment-resistant depression.[25,74–76] In 2005, Rumi et al[74] investigated whether fast (5 Hz) rTMS combined with amitriptyline enhances the drug efficacy. In a sample of 46 patients they demonstrated that the active group had a significantly faster response when compared to the sham group. In a larger trial, with 99 patients, Rossini et al[25] addressed whether fast (15 Hz) rTMS combined with venlafaxine, escitalopram or sertraline enhanced the drug response. They found statistically significant positive results for all drugs as compared to control (in this case drug and sham rTMS). In 2007 a multi-center trial conducted by Herwig et al[75] investigated the efficacy of add-on 10 Hz rTMS with mirtazapine or venlafaxine in 127 patients which showed similar rates of response (31%) for both active and sham groups. Finally, in 2008 Bretlau et al[76] enrolled 45 patients to receive, either active or sham, fast rTMS combined with escitalopram and concluded that active treatment was superior to sham, with a large effect size of 0.70.

In a recent study Simpson et al addressed the cost-effectiveness of rTMS in major depression using data from previous multi-center studies and of a Sequenced Treatment Alternatives to Relieve Depression trial (STAR*D).[77]

The authors modeled the cost-effectiveness of rTMS considering different scenarios in which rTMS was combined with antidepressants after failure in 1, 2, or more than 2 drug trials, and comparing such association with different augmentation pharmacological strategies (antidepressant with mood stabilizer and atypical antipsychotic). Considering a base cost of US$300 per treatment session for rTMS, the authors demonstrated that rTMS is cost-effective considering QALY criteria and might be more cost-effective than determined psychopharmacological combinations.[78]

Discussion

The present study summarizes the main issues a clinician should consider on antidepressant use in major depression and other psychiatric disorders, ie, efficacy in acute-onset depression and in sustaining remission, tolerability in clinical practice – including safety and potential adverse effects, cost-effectiveness analysis, and an example of augmentation strategies using neurostimulation devices for patients failing to antidepressant trials.

Efficacy

The meta-analyses comparing drugs vs placebo showed antidepressants to be significantly superior to placebo, in both adult and geriatric patients with major depression in different clinical settings. The effects observed were consistent but modest. Kirsch et al[15] compared drug-placebo difference vs baseline depression severity and found that it is clinically significant (ie, a 3-point difference) only in severe depression, suggesting that antidepressant use to be limited to this particular subgroup of patients. In a later rebuttal article, Kirsch[79] comments further on the results of this meta-analysis. The main points being:

a) The strong effect of placebo response that might be stronger for depression than for other disorders.
b) The biased observation in clinical practice (one cannot differentiate the "pharmacological" part of the antidepressant drug response of the "nonpharmacological" response).
c) The small advantage for drug over placebo shows that antidepressants have a lower effect than claimed.

Table 4 Characteristics of each repetitive transcranial magnetic study (rTMS) study included

Author	Patients	Strategy	Antidepressant used	Main results
Rossini[25]	99	accelerating	Venlafaxine, escitalopram or sertraline	rTMS hastened response of all drugs
Rumi[74]	46	accelerating	Amitriptyline	rTMS hastened response of drug
Herwig[75]	127	accelerating	Mirtazapine or venlafaxine	active and sham groups showed similar response
Bretlau[76]	45	accelerating	Escitalopram	rTMS hastened response of drug
Su[65]	30	add-on	Various (TRD)	superior response rate in active group
Rossini[66]	50	add-on	Various (TRD)	superior response rate in the 100% MT group
Avery[67]	68	add-on	Various (TRD)	superior response rate in active group
Fitzgerald[68]	50	add-on	Various (TRD)	superior response rate in active group
Garcia-Toro[69]	30	add-on	Various (TRD)	superior response rate in both active groups
Anderson[70]	29	add-on	Various (TRD)	superior response rate in active group
Bortolomasi[71]	19	add-on	Various (TRD)	superior response rate in active group
Loo[72]	38	add-on	Various (TRD)	superior response rate in active group
Mogg[73]	59	add-on	Various (TRD)	no difference between groups

Notes: An "accelerating" strategy is when both interventions begin at the same time, to hasten a response. An add-on strategy is when rTMS is used as an augmentation strategy.
Abbreviation: TRD, treatment-resistant depression.

d) If the meta-analysis is based on flawed data, so are the trials that made drug approval possible.

Along these lines, Kirsch and Moncrieff[80] defended the position that the choice of statistical methods greatly influence the outcomes, eg, using response rates instead of mean change scores can inflate the results.

Nevertheless, one should mindful that all meta-analyses of pooled results from efficacy studies (ie, clinical trials whose design is controlled through strategies of randomization, double-blinding, and weekly visit) which are applied to a selected population that might not always be the same of clinical practice.[17] Such controlled design favors high placebo rates that might diminish drug-placebo difference by a "ceiling" effect, also they are focused in increasing internal validity and not external generality of results, in other words, to address drug efficacy (the therapeutic effect in ideal, controlled circumstances) and not drug effectiveness (the therapeutic effect in usual, clinical settings).

Another important issue not addressed by these studies is the specificity of antidepressant effects, in other words, whether the amelioration associated with the use of these drugs is a specific effect associated with the mechanisms underlying major depression or a general effect on central nervous system. The effects of antidepressants on other conditions, such as generalized anxiety, panic disorder, obsessive-compulsive disorder, and chronic pain might favor the later hypothesis.

The meta-analyses of drug–drug trials did not show any drug to be particularly effective when performing only direct comparisons. It should be underscored that the meta-analysis of Montgomery et al[45] which found escitalopram to be definitely superior than other antidepressants, did not use important drugs such as sertraline, fluoxetine, paroxetine, and citalopram and thus such conclusions should be interpreted with care. In addition, Cipriani et al[33] performing direct and indirect comparisons, observed that 4 drugs (mirtazapine, escitalopram, venlafaxine, sertraline) were superior to another 8 studied (buproprion, citalopram, duloxetine, fluoxetine, fluvoxamine, milnacipran, paroxetine, reboxetine). However, the authors also underscore the possibility of sponsorship bias, as 3 of the superior drugs are among the newest antidepressants (although meta-regression analysis did not confirm this possibility).

In addition, large pragmatic trials can also provide robust evidence for effectiveness. The STAR*D trial involved 23 participating-psychiatric centers and 18 primary clinics and found no clear superior antidepressant in terms of efficacy.[21] Therefore, it seems that more than aiming for a specific "superior" antidepressant drug the clinician should focus on tolerability, adherence, and treatment compliance.

Tolerability

Therefore, a critical part of clinician strategy when dealing with major depression is to know, understand, and take advantage of the side effects profile each drug presents. For example, mirtazapine might not be the first choice for overweight patients, or paroxetine for patients with sexual dysfunction. The lack of studies covering breast-feeding and abnormalities in lipid metabolism cannot give definitive conclusions on the most suitable antidepressant, as there is no compelling evidence that antidepressants alter lipid levels independent of their effect on weight gain. Moreover, it is possible that lipid levels and major depression are positively correlated and independent of antidepressant use.[81] Several antidepressants are known to pass into breast milk and thus to the baby; however, the evidence of safety is known for only a few drugs. Current guidelines recommend that the mother should take the antidepressant immediately after breastfeeding and prior to infant's sleep time to minimize peak concentrations.[82] Finally, although it seems that some drugs have less impact on sexual function than others (eg, sertraline and venlafaxine more than escitalopram or duloxetine) this adverse event is frequent and might be an important factor hampering compliance.[54]

The meta-analysis of Cipriani et al[33] aimed to systematically assess not only the efficacy of antidepressants but also their profile of side effects indexing using dropout rate, assuming that dropouts observed in clinical trials occurred due to side effects. This might indeed be a viable measurement, although other reasons could also have contributed to dropouts. In addition, no meta-analysis assessed patients' long-term treatment compliance. It is known that compliance in major depression is poor: the average length of antidepressant treatment is less than 6 months and 25% of patients do not inform their physician on stopping treatment.[83] Therefore, although it is still unclear whether there is an antidepressant associated with a better compliance, some studies suggest that compliance might be influenced by time it takes for the antidepressant to take effect and the tolerability of an antidepressant, along with other associated factors such as patient education, therapeutic alliance, and family education.[84,85]

The observation that sertraline and escitalopram were among the most tolerated – and also the most effective – antidepressants might suggest that they are suitable for first-line treatment of depression. However, it should be underscored, within the limitations of this type of meta-analytic

approach, that in a large pragmatic trial (STAR*D) that compared sertraline vs bupropion vs venlafaxine in patients with major depression (after a failed citalopram trial), no difference between drugs was found in several outcomes (efficacy, response and remission rates and score change, time to remission, side effects, adverse effects, and dropouts). To our knowledge no large pragmatic trial has compared escitalopram to other antidepressants, and therefore it should be kept in mind that the putative higher tolerability of escitalopram has yet to be tested in larger effectiveness trials.

Augmentation strategies

When antidepressant therapies fail, according to STAR*D, one third of patients remain clinically depressed after more than three failed trials.[77] In fact the definition of "treatment-resistant depression" varies, and although a recent review of clinical trials showed that such a concept is used to define a subgroup (15%–40%) of patients failing to achieve significant clinical improvement after at least two antidepressant trials,[86] other authors propose to quantify the degree of resistance[77] to better assess outcomes. Nevertheless, this subgroup of patients represents a particular challenge for the clinician, as response rates decay one level after each treatment fails,[77] thus demanding alternative strategies to manage depression symptoms. One option is the use of classic augmentation therapies, ie the combination of two antidepressants or one antidepressant combined to either lithium or thyroid hormone, as tested in the large pragmatic trial STAR*D. However, there is still room for improvement, considering other novel combination strategies, such as antidepressants associated with lamotrigine[87] or atypical antipsychotics.[88] Another option is to combine antidepressants with neurostimulation therapies, in our review we found that three of four trials and eight of nine trials showed positive results for rTMS as an add-on strategy and as an augmentation strategy, respectively. More studies are needed to determine whether or not there is a specific class of antidepressant that can achieve better results, and also in which populations this strategy should be targeted. However, considering the recent approval by the FDA for rTMS use in refractory depression and its virtually absence of side effects it is expected there will be an increasing interest for rTMS in the next years. Additionally tDCS might be another promising alternative, although the trial reviewed showed negative results another tDCS study enrolling drug-free patients (not included in this review) showed positive results: Boggio et al[37] for instance, found fluoxetine and anodal tDCS to have similar efficacy in patients with major depression.

Pharmacoeconomics

The main agenda of the National Institute of Health in both the current and in the following years will be health care reform.[89] One important issue being currently debated is whether universal health care coverage is possible and who will bear the costs; however it is clear that in order to achieve such a goal it is mandatory to spend resources in a controlled and organized way. Thus it will be increasingly important to the physician to evaluate the cost-effectiveness of a particular therapy. Unfortunately, pharmacoeconomics is a relatively new discipline and physicians together with health-policy makers are seldom trained on this field.[90] The studies reviewed reflect the absence of consensus in methodology. While some studies rely on bayesian analyses, using data from clinical trials, others studies aim to evaluate the impact of offering antidepressant drugs within the budget of local health systems. As a result, pharmacoeconomics study outcomes, in contrast to efficacy and tolerability studies, vary markedly from country to country, as important considerations, besides the drug cost itself, are its availability in local public health systems versus the availability of other antidepressants, the presence of generic brands, and also the overall costs of treatment (physician consultation, referral to specialist, hospitalization costs). Thus a drug economically suitable to use in one country might not be in another. Similarly, a study performed 5 years ago might not be applicable currently due to market differences and the introduction of generics in the market. In this context, the use of neurostimulation techniques might be an economically viable alternative, rTMS for example

Table 5 Summary of common side effects related to use of antidepressants

Side effect	Drug	Side effect	Drug
Nausea/vomiting	Venlafaxine	Increase in blood pressure	Venlafaxine
Dizziness	Venlafaxine	Somnolence	Trazodone
Sexual side effects	Sertraline, paroxetine, mirtazapine	Discontinuation syndrome	Paroxetine, venlafaxine
Weight gain	Mirtazapine, paroxetine	Suicidal behavior	Not enough evidence
Headache	Bupropion	Serotonin syndrome	All antidepressants
Insomnia	Bupropion	Drop-out rates	Fluovoxamine, reboxetine

might be more cost-effective than augmentation with atypical antipsychotic drugs in treatment-resistant depression, and tDCS, if proved effective, might be an affordable alternative in underdeveloped countries.[91] Therefore, although studies in pharmacoeconomics are currently methodologically inferior to the studies in efficacy, cost-effectiveness issues will probably increase in importance as public systems increase their participation in financing health care.

Limitations

In this review we assessed efficacy and tolerability of antidepressants by analyzing meta-analyses only. This is clearly a limitation as despite meta-analyses and systematic reviews often being considered the "best available evidence" they are dependant on the qualitative analysis of the trials included and the inclusion criteria of the meta-analyses used in our study.[92] Indeed meta-analyses vary with the inclusion of unpublished studies,[15] sponsorship bias,[93] and open-label studies.[94] For example, a recent review of antidepressant publication bias[95] found that 94% of published trials were positive although when nonpublished trials are included only 51% were positive. In this study we included many meta-analyses in order to show results from studies using different inclusion criteria.

In this study the meta-analysis that found escitalopram and sertraline to be the most effective/tolerable antidepressant was determined through both direct and indirect comparisons.[33] An indirect comparison is made when drug A is compared to drug C by pooling the effects of the two (or more) studies, ie, one comparing drug A with drug B together with another studying drug B with drug C but without a trial comparing drug A directly with drug C. Although such an approach is justified when head comparison trials are limited,[96] an indirect comparison considers a homogeneity assumption (patients belonging to the same population) as well as a similarity assumption (trials are similar for moderators of relative treatment effect). A recent review[97] of 88 meta-analyses using indirect comparisons, from 2000 to 2007, concluded that indirect comparisons can be unbiased if the assumptions of similarity and homogeneity are fulfilled; however further research on the topic is necessary. Within this context, meta-analyses using indirect comparisons might be a good approach when synthesizing data of head-to-head noninferiority trials, as they might produce less biased results.[98]

Conclusion

Although recent meta-analyses suggest that the antidepressants escitalopram and sertraline present the highest efficacy and tolerability rates among SSRIs and therefore should be regarded as first-line treatments for major depressive disorder, these findings were not observed in large pragmatic trials and in other meta-analyses using different statistical methods. Therefore, at the present time, neither meta-analyses nor large pragmatic trials provide robust evidence of superior efficacy for any specific antidepressant drug. More than trying to select the "superior" antidepressant the clinician should be aware of managing other aspects of antidepressant treatment, such as side effects, adverse effects, and pharmacological interactions. In fact, acknowledging the main side effects and tolerability of antidepressants allows physicians to tailor the most suitable drug for each patient. Cost-effectiveness issues should be kept in mind when adjusting these findings to local settings. Finally, when the depressed patient fails to respond to an antidepressant trial, other available options are to switch to another antidepressant, augment the treatment with an additional antidepressant, or uptitrate the drug dosage. Another alternative is to associate antidepressants with neuromodulation interventions, eg, ECT is a powerful augmentation strategy to treat depression, although associated with cognitive impairment in some cases, while rTMS has moderate efficacy yet it is virtually free of side effects, and further studies are necessary to address the role of tDCS in the treatment of major depression.

Disclosures

The authors declare no conflicts of interest.

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