Combination/augmentation strategies for improving the treatment of depression

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Abstract: Depression is a common and debilitating condition, with considerable impact for depressed individuals and a heavy burden for society. In spite of its prevalence, depression is underrecognized and under- or inappropriately treated. In spite of the large number of antidepressants available at the present time, they are far from ideal and all show a similar slow, and frequently, incomplete response. Thus, the need for new and better compounds is as urgent and compelling as ever. While waiting for the panacea of future antidepressants, clinicians have developed a variety of associations of several antidepressants or an antidepressant with a second different agent. This article reviews the various strategies adopted by clinicians in the hope of increasing the response rate of current antidepressants to obtain full remission and/or to overcome treatment-resistant depression.

Keywords: depression, combination, augmentation, treatment-resistance

Introduction

Although depression affects a substantial proportion of the population (Kessler et al 2003), this disease is underrecognized and, if diagnosed (APA 1994), is still frequently inadequately or inappropriately treated. Because of the high prevalence and chronicity of depression, a complete antidepressant response remains an important objective for clinicians and is still a key target for new drug development (Andrade et al 2003; Greenberg et al 2003). "Response" of a depressed patient to treatment is defined as at least a 50% reduction in depressive symptoms evaluated on a standard instrument, such as the Hamilton Depression Rating Scale (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS) (Frank et al 1991). Although clearly the symptoms of a "responder" are improved, he or she is not "cured" or in "remission", which is a total absence of all symptoms of depression. Operationally, this is usually defined as a level of depressive symptoms that fall below a threshold value such as a score of ≤ 7 on the 17-item HAM-D as recommended by Frank et al (1991). It is generally accepted that about two thirds of patients treated for depression will respond to some extent albeit after several weeks (2–8 weeks) (Bosker et al 2004) and a third will not respond at all (Pérez et al 2001). Full remission, when it occurs (in about 30%–50% of treated patients), can take 4–6 weeks up to months to achieve (Rush and Trivedi 1995; Ferrier 1999). Despite the diversity of their mechanisms of action, all current antidepressants produce approximately the same final rates of response and remission (Artigas et al 2002). These figures speak for themselves, and the need for strategies to increase the response rate of patients and to obtain full remission in as many patients as possible is clear.

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When patients do not respond or respond insufficiently to monotherapy, numerous approaches have been attempted, some of which seem to be quite effective (Kelsey 2002; Thase 2004). These include "switching strategies" (within an antidepressant class or between drug classes, electroconvulsive therapy, and psychotherapy); "combination strategies", which involve the use of two or more different antidepressants together; or "augmentation strategies", consisting of the addition of a non-antidepressant therapy to a partially active therapy. These many treatment options for partially or totally refractory depression are often based on present neurobiological understanding of depression or the mechanisms of action of antidepressants. Many more are used in clinical practice, some with a theoretical basis, others purely empirically.

The main pharmacological classes of antidepressants include enzyme inhibitors (monoamine oxidase inhibitors [MAOIs]), uptake blockers, and receptor blockers. By dissecting these classes it is possible to reveal distinct mechanisms of action through which the antidepressants exert their therapeutic effect on depression when used as monotherapy (Lieberman et al 2005) (Table 1). The principal drugs belonging to each group of mechanism of action are indicated in Table 1.

Antidepressant combinations

The aim of combining antidepressants is to combine two or more mechanisms of action in an attempt to obtain a synergy (enhancement of efficacy) or enhanced tolerability (by opposing or blocking side effects).

Serotonergic strategy

Extensive inhibition of the reuptake of serotonin (5-hydroxytryptamine [5-HT]) can produce a range of serotonergic side effects experienced by some patients taking selective serotonin reuptake inhibitors (SSRIs). Associating extensive inhibition of 5-HT reuptake with antagonism of $5-HT_2$ receptors is an example of pharmacological synergy within the serotonergic system. In the combination of SSRIs with trazodone or nefazodone, the blockade of $5-HT_{2A}$ receptors can be beneficial since stimulation of $5-HT_{2A}$ receptors (through increased synaptic 5-HT) is responsible for the side effects such as agitation and insomnia (see retrospective prescription analysis of Clark and Alexander 2000). Blockade of $5-HT_{2A}$ receptors by trazodone reduces the incidence of these adverse events making it possible to increase the dose of SSRIs and boost their efficacy (Stahl 2000).

Table 1 Different antidepressants classified according to their mechanism of action

MAOIs: Irreversible and nonselective	Phenelzine
	Tranylcypromine
	Isocarboxazid
MAOIs: Reversible inhibitor of MAO-A	Moclobemide
MAOIs: Preferential inhibitor of MAO-B	Deprenyl[a]
Tricyclic (and tetracyclic) antidepressants	Clomipramine
	Imipramine
	Amitriptyline
	Nortriptyline
	Protriptyline
	Maprotiline
	Amoxapine
	Doxepin
	Desipramine
	Trimipramine
Selective serotonin reuptake inhibitors	Fluoxetine
	Sertraline
	Paroxetine
	Fluvoxamine
	Citalopram
	Escitalopram
Selective noradrenaline reuptake inhibitors	Reboxetine
	Atomoxetine
Noradrenaline and dopamine reuptake inhibitor/releaser	Bupropion[b]
Serotonin and noradrenaline reuptake inhibitors	Venlafaxine
	Milnacipran
	Duloxetine
Serotonin antagonists/reuptake inhibitors	Nefazodone
	Trazodone
Alpha$_2$-adrenoceptor antagonist	Mirtazapine
Electroconvulsive therapy	
Psychotherapy	

[a] Deprenyl at high doses also inhibits MAO-A and results in an antidepressant action.
[b] Recent studies indicate that bupropion may act more by enhancing the release of noradrenaline and dopamine than by blocking their reuptake (Dong and Blier 2001; Gobbi et al 2003).

Noradrenergic strategy

Noradrenergic neurotransmission needs to be boosted in some depressed patients, especially those with fatigue, apathy, and mental and physical slowing. Theoretically a noradrenergic boost can be expected by combining the noradrenaline reuptake inhibitor (NRI), reboxetine, or desipramine (tricyclic antidepressant [TCA] with a selective noradrenaline reuptake inhibition) with bupropion, a noradrenaline and dopamine reuptake inhibitor/releaser. As yet, however, there are no published studies to support this strategy (Stahl 2000).

Serotonergic and noradrenergic (and dopaminergic) strategy

A randomized, double-blind study has shown a greater remission in patients with major depression when combining the SSRI, fluoxetine, and desipramine than with either selective agent alone (Nelson et al 2004). For a subset of depressed patients, the most refractory depressed patients, activation of multiple neurotransmitter systems is beneficial in achieving remission (Kelsey 2002). In such cases, stimulating both serotonin and noradrenaline neurotransmission may be useful. Combinations of the serotonin and noradrenaline reuptake inhibitor (SNRI), venlafaxine, with mirtazapine can achieve this result in the various treatment options of the prospective, randomized trial described by Rush et al (2004). Mirtazapine, through its α_2-adrenoceptor blockade, potentiates noradrenaline activity, while its 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptor antagonisms limit serotonergic side effects.

A full list of potential double (or triple)-boost 5-HT, noradrenaline, and/or dopamine combinations are given in Stahl (2000).

An example of a serotonergic and noradrenergic and dopaminergic strategy is the combination of bupropion-SR (slow release) with the SSRI, citalopram, in a naturalistic, open-label cohort study (Lam et al 2004). Patients with major depression who had not responded to at least 6 weeks of treatment with citalopram or bupropion-SR were treated by a combination of citalopram and bupropion-SR. The combination was superior to either monotherapy in these treatment-resistant depressed patients (Lam et al 2004). Greater improvement has also been found in patients with affective illness who were treated with a combination of bupropion and a SSRI than with either agent alone (uncontrolled clinical series, Bodkin et al 1997). In depressed patients who partially responded to lithium augmentation (see below) of SSRI, the further addition of a noradrenergic antidepressant, bupropion or desipramine, substantially improved their symptoms (open case series, Ramasubbu 2002).

Other strategies
Electroconvulsive therapy

Electroconvulsive therapy (ECT) is highly effective for treatment of major depression, but a high rate of relapse after discontinuation of ECT is observed (Sackheim et al 2001). A small, retrospective case-controlled study by Gagné et al (2000) has shown that following an acute phase of ECT, maintenance ECT plus long-term antidepressant treatment was more effective than an antidepressant alone.

Psychotherapy

Interpersonal and cognitive behavioral therapies have been the best empirically supported treatments (for review, see Chambless and Hollon 1998). Evidence is accumulating that psychotherapy is most effective when combined with antidepressants. Cognitive or interpersonal therapy added to pharmacotherapy has been found to enhance the rate of remission for patients suffering from chronic (randomized comparative study, Keller et al 2000), severe recurrent (meta-analysis, Thase et al 1997; randomized comparative 2-year follow-up study, Fava et al 1998), resistant (open 2-year follow-up trial, Fava et al 1997), or partially treatment-responsive depressive syndromes (randomized comparative 2-year follow up study, Fava et al 1994; controlled trial, Paykel et al 1999). This approach was particularly useful in a fragile population of elderly depressed patients who received maintenance therapy with nortriptyline and interpersonal therapy that resulted in the best prophylaxis against recurrent episodes (randomized, double-blind, placebo-controlled trial, Reynolds et al 1999).

SAME (S-adenosyl-l-methionine)

Depressed patients who were partial and nonresponders to SSRIs (fluoxetine, paroxetine, citalopram, escitalopram, or sertraline) or the SNRI venlafaxine had their therapy supplemented with S-adenosyl-l-methionine (SAME). A response rate of 50% and a remission rate of 43% were obtained suggesting that the combination of SAME with antidepressants might be an effective strategy in resistant depression (open trial, Alpert et al 2004).

Augmenting agents
Lithium and mood stabilizers

Lithium has been used for many years in the treatment of bipolar disorder to control mania, and it has also proven to be an effective adjunct to standard antidepressants in the acute treatment phase of unipolar major depression (see review of Bauer et al 2003). Studies have shown that lithium can increase response or initiate response in nonresponders when used in association with different types of anti-depressants such as TCAs, MAOIs, SSRIs, and the SNRI venlafaxine (open trial, Bertschy et al 2003). Lithium augmentation has also demonstrated to be effective in the continuation treatment phase to prevent early relapse. It is

thought to act on various neurotransmitter systems at the level of signal transduction mechanisms, leading to neuroplastic changes associated with stabilization of mood (see the review of Lenox and Hahn 2000). Lithium also plays a correcting role in the expression of some genes involved in the pathophysiology of bipolar disorder. Animal studies have shown that potentiation of antidepressant treatment by lithium may also be mediated through enhanced 5-HT neurotransmission (Haddjeri et al 2000). Neuroendocrine studies in humans also demonstrate that lithium augments the function of the serotonergic system (Bauer et al 2003).

Although mood stabilizers are usually prescribed with antidepressants to avoid switching to mania in bipolar patients, some are used as augmentation agents in depression. Anticonvulsants, such as valproate, carbamazepine (see review of Dietrich and Emrich 1998), and lamotrigine (randomized, double-blind, placebo-controlled study, Barbosa et al 2003), combined with classical antidepressants appear to be well tolerated and effective in treatment-resistant depressed patients. Recently, venlafaxine combined with carbamazepine has proved to be effective in the treatment of depressed patients not responding to monotherapy with venlafaxine (open study, Ciusani et al 2004).

Thyroid hormone

The prevalence of thyroid dysfunction in women is high. Hypothyroidism is associated with depression, and correcting this endocrine dysfunction is beneficial when treating an associated depression (Larisch et al 2004). The addition of triiodothyronine (T3) to ongoing TCA treatment is an effective augmentation strategy in patients with refractory depression in a randomized, double-blind, placebo-controlled study (Joffe et al 1993) and in accelerating clinical response to TCAs in patients with nonrefractory depression, particularly women (meta-analysis, Altshuler et al 2001). For example, depressed patients unresponsive to the SSRI fluoxetine, responded to fluoxetine associated with T3 (open-label treatment, Agid and Lerer 2003). This augmentation effect of T3 on the antidepressant action (at least of the tricyclics) may be explained by the increased 5-HT levels in rat frontal cortex after chronic administration of T3, measured by microdialysis (Gur et al 1999). Chronic administration of clomipramine also resulted in increased levels of 5-HT in the frontal cortex. In rats treated with clomipramine and

T3, cortical levels of 5-HT were higher than those of rats receiving only one treatment (Gur et al 1999).

5-HT$_{1A}$ receptor augmenting agents

Clinical studies and genetic research in animals and humans have suggested that the activity of 5-HT$_{1A}$ receptors may be important in the pathophysiology of depression (Celada et al 2004; Neumeister et al 2004). The somatodendritic 5-HT$_{1A}$ autoreceptors located in the raphe nuclei are stimulated by increased serotonin concentrations that result from the inhibition of serotonin reuptake by antidepressants such as SSRIs given acutely. This results, through a negative feedback mechanism, in an inhibition of the firing activity of midbrain 5-HT neurones and the release of 5-HT by terminals in the forebrain. This leads to an attenuation of the increase in synaptic 5-HT produced by antidepressants in forebrain. The delayed onset of action of serotonergic antidepressants is considered to be, at least in part, the result of a reduction in the function, or desensitization, of 5-HT$_{1A}$ somatodendritic autoreceptors, which occurs following chronic treatment with these drugs. This delay of onset of action is similar to the time necessary for the desensitization of these 5-HT$_{1A}$ autoreceptors by the SSRIs to occur (Blier and de Montigny 1994).

5-HT$_{1A}$ receptor antagonists

As explained above, only when the 5-HT$_{1A}$ autoreceptors are desensitized (after several weeks) is the full potential of serotonin reuptake inhibition obtained. The 5-HT$_{1A}$ receptor antagonists can remove this feedback and have been proposed as a means of accelerating and possibly potentiating antidepressant action (Pérez et al 2001; Serrats et al 2004).

The β-adrenergic/5-HT$_{1A}$ receptor antagonist, pindolol, which binds to the 5-HT$_{1A}$ receptors in the human brain (Martinez et al 2001; Rabiner et al 2001), accelerates and may enhance the antidepressant effect of SSRIs (meta-analysis of Ballesteros and Callado 2004; review of Isaac 2004), such as fluoxetine (see review of Artigas et al 2001; controlled trial, Pérez et al 2001), or in paroxetine-refractory patients (placebo-controlled study, Sokolski et al 2004). Not all authors, however, have been able to replicate these findings (double-blind, placebo-controlled trial, Berman et al 1997). Preclinical studies that have examined the desensitization hypothesis and clinical studies that utilized pindolol as a test of this hypothesis in depressed patients have been reviewed by Kinney et al (2000).

Buspirone

The partial 5-HT$_{1A}$ receptor agonist (full agonist at 5-HT$_{1A}$ autoreceptors and partial agonist at postsynaptic 5-HT$_{1A}$ receptors) buspirone, which is used principally in generalized anxiety disorder, has also been shown to produce marked clinical improvement when used as an augmenting agent in depressed patients who are initially unresponsive to the SSRIs such as fluoxetine, paroxetine, or citalopram (open trial, Dimitriou and Dimitriou 1998; see review of Shayegan and Stahl 2000). Results from a randomized, double-blind, placebo-controlled study showed that severely depressed patients had a better response when buspirone (compared with placebo) was added to their fluoxetine or citalopram treatment (Appelberg et al 2001). However, another double-blind, placebo-controlled trial (Landen et al 1998) failed to demonstrate any difference in the extra efficacy resulting from the addition of buspirone or placebo to their SSRI therapy. An unusually high placebo response may explain this result.

The effect of buspirone is thought to be via enhancement of the activation of postsynaptic 5-HT$_{1A}$ receptors in the presence of 5-HT$_{1A}$ autoreceptors, which have already been desensitized by the antidepressant.

Estrogen

Vulnerability to mood disorders is increased during perimenopause and postmenopause (Soares and Cohen 2001). Because fluctuating estrogen levels accompany the perimenopausal transition, estrogen replacement therapy (ERT) has been suggested as a possibly effective adjunctive treatment for mood disorders occurring during peri-menopause (Soares and Cohen 2001). Discontinuation of hormone therapy appears to be associated with the rapid recurrence of depression in some women with a history of depression (Stewart et al 2004). Small studies have shown that in depressed women who have minimal response to a SSRI, ERT may augment response (open trial, Rasgon et al 2002; randomized comparative study, Westlund and Parry 2003). Fluoxetine combined with ERT in a recent randomized, open-label, parallel trial was effective in the treatment of menopausal depressed women (Liu et al 2004).

Inhibitors of steroid synthesis

Young et al (2004) have reported that the corticosteroid receptor antagonist mifepristone can exert an antidepressive effect. Following these preliminary results, Jahn et al (2004) have shown in a double-blind, placebo-controlled trial that metyrapone, an inhibitor of cortisol synthesis and associated with nefazodone or fluvoxamine, gives a better outcome than the antidepressants alone, with an earlier onset of action and a sustained effect in patients with major depression.

Methylphenidate

The antidepressant response to monotherapy is often inadequate in the elderly and especially in patients with extensive psychomotor slowing. The addition of a stimulant action can be particularly beneficial in this fragile population by accelerating and intensifying the response. The indirect dopaminergic agonist and psychostimulant methylphenidate (for review, see Leonard 2004) combined with MAOIs still represents an alternative after other options have failed (see review of Feinberg 2004; case study, Shelton Clauson 2004). Methylphenidate has also been shown by Lavretsky et al (2003) in an open-label trial to accelerate the response to the SSRI citalopram in this population.

Atypical antipsychotics

In subjects with recurrent major depression (non-bipolar) without psychotic features and who are unresponsive to conventional antidepressant therapy, it has been demonstrated that the efficacy of olanzapine plus fluoxetine is superior for treating their resistant depression than either agent alone (double-blind, comparative study, Shelton et al 2001; retrospective chart review, Barbee et al 2004). Similar results were obtained with ziprasidone in association with the SSRIs, fluoxetine, paroxetine, citalopram, or sertraline (Barbee et al 2004; open trial, Papakostas et al 2004). An augmentation therapy of milnacipran with risperidone has been found to considerably improve recovery in patients with depression who only partially responded to milnacipran alone, and also in some treatment-refractory patients (case series, Tani et al 2004). In addition, the response to the addition of risperidone was very rapid (less than 5 days), in agreement with previous reports (case series, Ostroff and Nelson 1999; Shelton et al 2001). This augmentation effect is thought to result in part from the blockade of 5-HT$_{2A}$ receptors and may be explained by the results of animal studies. The combination of olanzapine and other antipsychotics with the SSRI fluoxetine produced robust, sustained increases of extracellular levels of dopamine and noradrenaline in rat prefrontal cortex and hypothalamus as measured by microdialysis, greater than with either drug alone (Zhang et al 2000; Koch et al 2004). Blocking simultaneously the 5-HT transporter and 5-HT$_{2A}$ receptors

Table 2 List of combination/augmentation strategies

Antidepressants	Adjunct	Supposed mechanism of action	Type of study (reference)
Antidepressant combinations			
SSRIs	Trazodone Nefazodone	Prevention of side-effects by blockade of 5-HT$_{2A/C}$ receptors	Retrospective prescription analysis (Clark and Alexander 2000)
Reboxetine Desipramine	Bupropion	Catecholamine boost	Review (Stahl 2000) (theoretical)
Venlafaxine	Mirtazapine	5-HT and NA boost	Prospective and randomized trial (Rush et al 2004)
SSRIs	Bupropion-SR	5-HT, NA and DA boost	Naturalistic, open-label cohort study (Lam et al 2004) Uncontrolled clinical series (Bodkin et al 1997); open case series (Ramasubbu 2002)
Various	ECT	Probably stimulation of common pathways	Retrospective case-controlled study (Gagné et al 2000)
Various	Psychotherapy	Probably stimulation of common pathways	Randomized, comparative study (Keller et al 2000); meta-analysis (Thase et al 1997); randomized, comparative 2-year follow-up study (Fava et al 1998); open 2-year follow up trial (Fava et al 1997); randomized, comparative 2-year follow up study (Fava et al 1994); controlled trial (Paykel et al 1999); randomized, double-blind, placebo-controlled trial (Reynolds et al 1999)
SSRIs Venlafaxine	SAME	DA boost	Open trial (Alpert et al 2004)
Augmentation strategies			
TCAs MAOIs SSRIs Venlafaxine	Lithium Valproate Carbamazepine Lamotrigine	Second messenger system boost 5-HT boost	Review (Bauer et al 2003); open trial (Bertschy et al 2003); review (Dietrich and Emrich 1998); randomized, double-blind, placebo-controlled study (Barbosa et al 2003); open study (Ciusani et al 2004)
TCA Fluoxetine	Thyroid hormone	Correction of endocrine dysfunction	Randomized, double-blind, placebo-controlled study (Joffe et al 1993); meta-analysis (Altshuler et al 2001); open-label treatment (Agid and Lerer 2003)
Fluoxetine Paroxetine	Pindolol	Blockade of 5-HT$_{1A}$ autoreceptors (feedback removal)	Meta-analysis (Ballesteros and Callado 2004); review (Isaac 2004); review (Artigas et al 2001); controlled trial (Pérez et al 2001); placebo-controlled study (Sokolski et al 2004); double-blind, placebo-controlled trial (Berman et al 1997)
Fluoxetine Paroxetine Citalopram	Buspirone	Stimulation of postsynaptic 5-HT$_{1A}$ receptors	Open trial (Dimitriou and Dimitriou 1998); review (Shayegan and Stahl 2000); randomized, double-blind, placebo-controlled study (Appelberg et al 2001); randomized, double-blind, placebo-controlled study (Landen et al 1998)
Fluoxetine	Estrogen	Correction of estrogen fluctuations	Open trial (Rasgon et al 2002); randomized, comparative study (Westlund and Parry 2003); randomized, open-label, parallel trial (Liu et al 2004)
Nefazodone Fluvoxamine	Metyrapone	Inhibition of cortisol synthesis (high in depression)	Double-blind, placebo-controlled trial (Jahn et al 2004)
MAOIs Citalopram	Methylphenidate	DA boost	Review (Feinberg 2004); case study (Shelton Clauson 2004); open-label trial (Lavretsky et al 2003)
Fluoxetine Paroxetine Citalopram Sertraline Milnacipran	Olanzapine Ziprasidone Risperidone	Blockade of 5-HT$_{2A}$ receptors Stimulation of 5-HT$_{1A}$ receptors NA boost	Double-blind, comparative study (Shelton et al 2001); retrospective chart review (Barbee et al 2004); open trial (Papakostas et al 2004); case series (Tani et al 2004); case series (Ostroff and Nelson 1999)

Abbreviations: DA, dopamine; ECT, electroconvulsive therapy; NA, noradrenaline; SAME, S-adenosyl-l-methionine; SSRIs, selective serotonin reuptake inhibitors.

has also been shown to enhance synaptic availability of noradrenaline using in vivo extracellular unitary recordings (Szabo and Blier 2002). Many atypical antipsychotics also possess 5-HT$_{1A}$ receptor agonist properties. It is possible that this characteristic may play a role especially when associated with an increase in the release of noradrenaline and dopamine in the prefrontal cortex when antipsychotics are combined with the SSRIs (Papakostas et al 2004).

Conclusion

Approximately, eight classes of antidepressants acting by distinct pharmacological mechanisms including over 20 compounds are available to the clinician for the treatment of depression. The potential combination of any two compounds is therefore high, which makes for a very impressive armamentarium to treat depressed patients who do not respond to antidepressant monotherapy. The exact nature of the depressive disorder and the type of symptoms can guide the clinician in choosing the first treatment. The use of an algorithm can also provide help for adapting and managing the best combination for a given individual. Certain combinations such as a MAOI with a drug that blocks serotonin reuptake should never be used because of the high risk of inducing a serotonin syndrome (Bijl 2004). Unfortunately, some combinations and most augmenting strategies are often based on case reports, very small, open pilot trials, or even anecdotal findings, which would merit replication in larger controlled trials. A summary of combinations and augmentations presented here is given in Table 2. Lithium, thyroid hormone, and buspirone, which have been used for a long time, have been the three most studied combinatory agents. Some of the newer compounds are promising since they provide ways of boosting neurotransmission or reducing negative adverse effects allowing increased doses of the accompanying anti-depressant. The increased use of this panoply of drug combinations will hopefully make it easier for clinicians to overcome the treatment-resistant depression and reach full recovery in a larger number of patients. The problem is that there is a lot of rather unstructured data suggesting benefit from various approaches, but there are very few comparisons between these approaches. The National Institute of Mental Health Sequenced Treatment Alternatives to Relieve Depression (STAR*D) program is an ambitious research initiative that is intended to generate a much needed treatment algorithm (Lavori et al 2001; National Institute of Mental Health 2003; Rush et al 2004). In this study,

approximately 4000 depressed patients will begin treatment with citalopram at doses up to 60 mg per day. If there is an inadequate response, they will be randomly assigned to a variety of treatment options: alternative SSRIs (sertraline), SNRI (venlafaxine), cognitive therapy alone, or continuation citalopram with the addition of cognitive therapy, buspirone, or bupropion augmentation. In case of no response, the next step of therapy will include switching to nortriptyline or mirtazapine, or augmentation with lithium or thyroid hormone. A final phase for ultimate nonresponders will be random assignment to either tranylcypromine or combined venlafaxine and mirtazapine. Hopefully, this program should provide good comparative data and make the clinician's choice easier.

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