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Antidepressant Treatment Selection and Treatment Resistant Depression

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Depression is a common medical illness with staggering public healthcare implications. The World Health Organization estimates that by 2020, unipolar depression will be the leading cause of disability in the world.[1] In addition, recent estimates calculate a cost of at least $44 billion dollars in related direct expenses and productivity loss associated with depression in the United States.[2] Antidepressant medications have become a standard of care in the treatment of major depressive disorder. This article will explore antidepressant treatment selection and treatment alternatives in treatment-refractory depression. Initial choice of antidepressant medication includes the following factors:

- *Lack of evidence showing difference in effectiveness* - Well-known treatment guidelines and large scale meta-analyses suggest that efficacy is similar between all antidepressant medications.[3,4] In addition, antidepressant treatment algorithms recommend that all newer antidepressants (e.g. SSRIs, SNRIs, bupropion) can be used first-line.[5] Therefore, other factors come into play when considering first-line choice of an antidepressant for a particular patient.

- *Personal/family history*—Knowing which medication the patient has responded to in the past, or which medication has been used to successfully treat a relative of the patient can help predict a positive clinical response.

- *Side effect profiles (and patient preference*)—All antidepressants have side effects, some more bothersome than others. Some side effects, such as sedation or appetite stimulation, may be useful early in treatment but cause problems later in treatment when the patient has recovered. Still other side effects, such as sexual dysfunction, may be of little consequence for a depressed patient but may interfere with functioning after recovery. Planning for these side effects and discussing options with patients may increase medication adherence for both the short and long term.

- *Ease of use*—Medications that only require once-daily dosing are often easier for patients than medications that require multiple doses during the day..

- *Cost*—Lower cost generic antidepressants (e.g. citalopram, sertraline) are therapeutically similar to their brand name counterparts and are excellent first choices. Using dose consolidated or tablet-splitting regimens can also lead to significant cost savings.[6] Table 2 provides a cost comparison of frequently used antidepressant medications.

The goal of antidepressant treatment should be established at the start of treatment and reassessed throughout its course. Most traditional depression studies have focused on clinical efficacy. In these clinical trials, generally healthy volunteers are treated for relatively short periods of time and their response rates (i.e. reduction of >50% in baseline symptoms) are compared to a control group. Information from these studies does not often translate well into clinical practice. Instead, the goal of depression treatment should be centered on remission, or the virtual absence of symptoms (as measured by a HAM-D score less than or equal to 7). Remission is associated with better long-term prognosis and functionality.[2]

Many patients will not achieve remission with their first trial of antidepressant medication. Studies providing guidance for treatment resistant depression (TRD) (defined as the failure to achieve remission after an adequate antidepressant medication trial) have been limited. Information from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study provides a better understanding of the prevalence of TRD and offers guidance for treatment alternatives.[2] The STAR*D study, funded by the National Institute of Mental Health (NIMH), was a multicenter, prospective, sequentially randomized controlled trial of outpatients with nonpsychotic unipolar depression. This "real world" trial allowed for the comparison of switching medications or medication augmentation strategies and incorporated clinician and patient preference. The study found that after an adequate trial of a selective serotonin reuptake inhibitor (Level 1), 70% of patients did not experience a complete remission of symptoms. Higher rates of remission were associated with patients who were: female, Caucasian, higher education level, marriage or cohabitation, employed, insured, shorter current episode, and fewer concurrent general medical or psychiatric disorders. Of the 30% of patients who did experience remission, 33.5% had a relapse of depressive symptoms within the 12-month follow-up period.

During the second level of the STAR*D trial, patients with an unsatisfactory response to the SSRI were given the opportunity to augment therapy or switch to a new antidepressant. Only 25% of patients who switched therapy (to either another SSRI, bupropion SR, or venlafaxine XR) achieved remission. There were no significant differences in remission rates, tolerability, or side-effect burden among the antidepressants. Also of importance, this study found that intolerance to or lack of efficacy with the first SSRI did not portend intolerance or lack of efficacy with the second SSRI. In the augmentation phase, approximately 30% of patients treated with either bupropion-SR or buspirone in addition to their initial SSRI achieved remission. The study authors concluded that agumentation with bupropion-SR was preferred over buspirone because of greater reduction in measured depression symptoms from baseline and fewer overall side effects. Of those who achieved remission in this second level of treatment, 47.4% ended up having a relapse.

During level 3, patients who did not achieve remission in level 2 could agree to augment their current antidepressant (with lithium or T3) or switch to a different antidepressant (mirtazapine or nortriptyline). Remission rates did not differ significantly between mirtazapine and nortriptyline (12.3% and 19.8% respectively). The study authors suggest there may be only limited utility to three sequential trials of antidepressant monotherapy. Similarly, the rates of remission for both lithium and T3 appeared to be similar (15.9% and 24.7% respectively). The study authors did slightly favor T3, however, primarily because of slight advantages in effectiveness and tolerability, and the lack of need for blood level monitoring. Overall, a total of 13.7% of level 3 patients achieved remission. Total relapse rate for all successful level 3 treatments was 42.9%.

Level 4 patients could either participate in monoamine oxidase inhibitor therapy (MAOI) (tranylcypromine) or combination therapy with venlafaxine XR and mirtazapine. Remission rates for both groups were low with only 6.9% of the tranylcypromine group and 13.7% of the combination treatment group achieving remission (overall remission rate between the two groups equaled 13%). Due to a more favorable side effect profile and the lack of dietary interactions, the authors favored the combination of venlafaxine XR and mirtazapine over the MAOI. Low remission rates for both groups suggested that switching antidepressant medication after failure to achieve remission with three previous medication trials provides only limited chance for success.

The findings from the STAR*D trial (summarized in Table 1) suggests the following key clinical insights:

- TRD is highly prevalent
- Self-monitoring tools for symptoms and side effects should be adopted into routine clinical practice
- Measurement-based treatment protocols promote objectivity in the selection of treatment for depression and TRD
- Longer courses of treatment (12 to 14 weeks) may be necessary for patients who initially fail to respond to the prescribed therapy
- Remission, rather than response, should be the goal of antidepressant therapy

Table 1. Remission, relapse and intolerance findings from the STAR*D trial.

Level	Remission Rate	Relapse Rate	Intolerance Experienced
Level 1 (n=3671)	36.8%	33.5%	16.3%
Level 2 (n=1439)	30.6%	47.4%	19.5%
Level 3 (n=390)	13.7%	42.9%	25.6%
Level 4 (n=123)	13.0%	50.0%	30.1%

Although initial antidepressant treatment selection includes a number of factors, all newer generation antidepressant are considered equally effective and suitable first-line alternatives.[5,6] With the awareness that the overall goal of antidepressant treatment is a complete remission of depressive symptoms, clinicians are faced with a high prevalence of treatment resistant depression. The need for better understanding of the TRD disease process and improved treatment is undeniable.

Table 2. Antidepressant Cost Comparison Table

Antidepressant	Cost/30 days*
Amitriptyline	$2
Citalopram	$5
Fluoxetine	$11
Mirtazapine	$22
Paroxetine	$38
Bupropion SR	$73
Sertraline	$8
Lexapro	$89
Venlafaxine	$93
Bupropion XL	$96
Paxil CR	$122
Effexor XR	$159
Pristiq	$109
Cymbalta	$152

*Average retail cost for 30-days to OHP, June 2008. Excludes Rebate

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References:

[1] Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020. Global Burden of Disease Study. *Lancet.* 1997;349:1498–504.

[2] Cain RA. Navigating the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study: practical outcomes and implications for depression treatment in primary care. *Prim Care Clin Office Pract*. 2007;34:505–519

[3] Karasu TB, Gelenberg A, Merriam A, et al. Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Second Edition. Work Group on Major Depressive Disorder. Available at http://www.psychiatryonline.com/content.aspx?aid=48690. Accessed June 12, 2008.

[4]Gartlehner G, Hansen RA, Kahwati L, et al. Drug Class Review on Second Generation Antidepressants, 2006. Available at http://www.ohsu.edu/drugeffectiveness/reports/final.cfm. Accessed June 12, 2008.

[5] Texas Department of State Health Services. TMAP Algorithms. Strategies for the Treatment of

Major Depression (Nonpsychotic), version 3. Available at http://www.dshs.state.tx.us/mhprograms/Disclaimer.shtm. Accessed June 12, 2008.

[6] Hamer AM, Hartung DM, Haxby DG, et al. Initial Results of the Use of Prescription Order Change Forms to Achieve Dose Form Optimization (Consolidation and Tablet Splitting) of SSRI Antidepressants in a State Medicaid Program. J Manag Care Pharm. 2006;12(6):449-56.