

# 11. Psychopharmacological Intervention

## 11.1 Goals of Psychopharmacology

The goal of psychopharmacology is to ensure that patients with more severe forms of depression and those who fail to benefit adequately from the ENRICHD CBT/Group intervention are provided the full range of therapeutic options for depression. Although it is important to optimize patients' opportunity to achieve full resolution of depression, it is essential to safeguard the intent of ENRICHD to examine the effectiveness of psychosocial interventions in post-MI depression and social isolation. Thus, there is an incentive to impose a relatively high threshold for instituting psychopharmacology at the time of intake and randomization. Simultaneously, the need to ensure rapid remission of depression, to mitigate the presumed post-MI risks, argues for a low threshold for considering psychopharmacology if the response to CBT/Group is inadequate.

For these reasons, the criterion adopted for considering psychopharmacology at intake represents severe depression (Hamilton Depression Scale score  $\geq 24$ ), which the clinical literature suggests may require either pharmacotherapy or a combination of psychotherapy and drug therapy for an optimal treatment response (AHCPR Clinical Practice Guidelines: Treatment for Major Depression, 1993). Employing this rather strict criterion, however, will ensure that the majority of ENRICHD patients will be provided an opportunity to benefit from the CBT/Group intervention alone.

Some depressed patients may not achieve an adequate response to CBT. As noted in the Individual Cognitive Behavior Therapy section of the Manual of Operations, patients with major depression who have not achieved at least a 50% reduction in BDI scores by the 6th week of CBT treatment will be referred to the study psychiatrist for consideration of antidepressant therapy. Treating psychotherapists should also consider referring patients for a psychopharmacology assessment at any time during treatment if, in their clinical judgment, the patient is not responding adequately to CBT.

Finally, socially isolated patients or depressed patients who are undergoing or have completed the CBT/Group intervention may develop major depression during the course of the intervention period and should be referred for psychopharmacology evaluation if moderately severe depression (HDS  $\geq 20$ ) is present or if the response to "refresher" CBT is deemed inadequate.

## 11.2 Eligibility for Psychopharmacology

Candidates for antidepressant treatment will:

1. Fulfill DSM-IV criteria for Major Depression

**and**

2. Score  $\geq$  24 on the **baseline** 17-item Hamilton Depression Scale rating

**or**

Have an inadequate response to individual CBT, i.e.,  $<$  50% reduction in BDI ratings after 5 weeks of therapy; be judged to have an inadequate response to CBT during "refresher" sessions following depression relapse

**or**

Score  $\geq$  20 on the 17-item Hamilton Depression Scale during the 12 month period after enrollment completing the CBT/Group therapy intervention

Candidates for antidepressant therapy will be referred to community providers for depression management rather than receive treatment by the ENRICHD psychiatrist if they fulfill any of the following criteria:

1. DSM-IV Major Depression with Psychosis
2. Judged to be a serious suicide risk (see MOO Depression Intervention)
3. Severe major depression requiring electroconvulsive therapy
4. Active alcohol or substance abuse
5. History of sensitivity to sertraline or other newer generation antidepressants.
6. Medical condition judged to be a contraindication to SSRI treatment (e.g., liver failure, drug-drug interactions)
7. Patient or primary physician/cardiologist unwillingness to accept pharmacological treatment

### 11.3 Evaluation of Patients who are taking Psychopharmacological Medications at the time of Enrollment.

The ENRICHD psychiatrist at each site needs to review the safety and apparent efficacy of any antidepressants used in patients on antidepressants at the time of enrollment. The review will occur through discussion of the case with the case-coordinator (or other individuals involved in the patient's assessment) and should occur within three weeks of enrollment.

1. Safety. The safety of the medication will be considered from a statement of potential harmful effects of the medication as used in patients with cardiovascular disease and interactions with other medications the patient may be taking. A decision to intervene with the treating physician will be based on the discretion of the local ENRICHD psychiatrist.
2. Efficacy. The efficacy of antidepressants the patient may be taking at the time of enrollment will be considered in terms of medication type, dose, length, and the patient's response. The decision to intervene (e.g., to call the local psychiatrist or other physician treating the patient) will be left with the local ENRICHD psychiatrist.

The ENRICHD psychiatrist should review the status of patients on medications at entry 3 and 6 months and more often as indicated.

### 11.4 Psychopharmacology Evaluation and Treatment Protocol

Patients will be referred to ENRICHD psychiatrists for evaluation and possible antidepressant treatment (with the exceptions noted above). Study psychiatrists will employ a standard history and diagnostic assessment to confirm the presence of the psychopharmacology eligibility criteria and will determine by appropriate physical examination or laboratory findings that depression symptoms are not attributable to underlying medical or metabolic conditions (e.g., hypothyroidism, electrolyte disturbances).

Informed consent for antidepressant treatment will be obtained.

Concurrence for initiating antidepressant treatment will be obtained from the patient's primary physician/cardiologist.

## 11.5 Sertraline Administration

Sertraline will be prescribed as the initial antidepressant for qualified patients. This agent was selected because it offers a preferred profile for safety and effectiveness in the treatment of major depression in the context of cardiovascular disease (Glassman et al, 1993; Preskorn et al, 1992; Preskorn et al, 1994; Preskorn et al, 1995; Ketter et al, 1995; Nemeroff et al, 1996). Patients with a history of sensitivity to or a prior lack of response to sertraline will be prescribed an alternative agent, according to the guiding principles described below.

Sertraline will be provided without charge, packaged in bottles of 30 scored tablets.

Patients will be evaluated weekly as needed and feasible for the first 3-5 weeks of treatment; thereafter, patients will be assessed at 2-4 week intervals as needed and as feasible.

The starting dose of sertraline will be 50 mg per day, given in the morning with meals. This dose will be maintained for at least 2 weeks. In the absence of dose-limiting adverse effects, the dose may be increased to 100 mg per day for 2 weeks and further increases, if necessary, to a maximum daily dose of 200 mg per day are permitted. In frail patients, sertraline treatment can be initiated at 25 mg per day for the first week, increasing the dose to 50 mg after one week as described above. Doses may be decreased at any time if necessary due to adverse effects. In the absence of an adequate therapeutic response, patients unable to tolerate 25 mg per day or unable to tolerate an increase to a higher dose after 4 weeks of therapy will be considered for alternative antidepressant treatment (see below).

Sertraline treatment will be maintained throughout the 12 month intervention period for patients who achieve a therapeutic response.

ENRICHD psychiatrists will monitor concomitant drug administration to identify possible drug incompatibilities, e.g., coumadin, terfenadine, and will alert the primary physician/cardiologist to the need to monitor anticoagulation status for patients receiving coumadin. The potential for drug-drug interactions is high in ENRICHD patients, who will likely be prescribed an array of cardiovascular agents. It is important that ENRICHD psychiatrists keep abreast of the rapidly evolving literature indicating that antidepressants possess potent, but variable, influences on the hepatic P450 isoenzyme systems determining the metabolic fate of many cardiac drugs (Preskorn et al, 1994; Preskorn et al, 1995; Ketter et al, 1995; Nemeroff et al, 1996).

Short-acting benzodiazepine hypnotics or anxiolytics (oxazepam, lorazepam, temazepam) or chloral hydrate will be permitted for short term use (3 - 14 days) when sleep or anxiety are causing significant distress or interfering with function. The amount and dose will be carefully recorded.

## 11.6 Alternative Antidepressant Treatment

Patients with a history of sensitivity to or a prior inadequate response to sertraline, those unable to tolerate sertraline due to emergent adverse effects, and those who fail to achieve an adequate response during the ENRICHD trial will be considered for alternative antidepressant treatment.

The selection of an alternative agent will be made at the discretion of the treating psychiatrist based upon the specific needs of each patient. Selection will be limited to the agents listed in Table 1 after

considering the potential advantages and disadvantages for each agent. Starting and maximum doses for each agent are provided in Table 2.

Starting doses will be maintained for at least 2 weeks. Smaller starting doses than those recommended in Table 2 may be employed for selected patients, if needed. In the absence of dose-limiting adverse effects, doses may be gradually increased over 2-4 weeks to the maximum recommended dose levels. Doses may be decreased at any time if necessary due to adverse effects. In the absence of an adequate therapeutic response, patients unable to tolerate the recommended starting dose or unable to tolerate an increase to a higher dose after 4 weeks of therapy will be referred to community providers for further management of their depression.

Alternative antidepressant medications will be prescribed at the patients' expense. Medication will be dispensed in the minimum quantity necessary to provide coverage for the interval between follow-up visits.

### **11.7 Psychopharmacology Maintenance and Termination**

The frequency of periodic follow-up assessments during the course of psychopharmacology will be determined at the discretion of the treating psychiatrist, with a minimum of at least monthly visits during the maintenance phase of psychopharmacology is maintained.

Patients who achieve a therapeutic response to antidepressant treatment will be maintained on medication for 12 months, at which time antidepressant therapy can be withdrawn. Patients who require extended psychopharmacology will be referred for further treatment in the community.

Rarely during the 12 month intervention period, patients might develop psychosis, be judged at risk for suicide, require hospitalization or otherwise require more intensive intervention than can be effectively provided by ENRICHD psychiatrists. Such patients will be referred for appropriate ongoing care in the community.

### **11.8 REFERENCES**

- Depression Guideline Panel: Depression In Primary Care. Vols. 1 and 2. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service; 1993. Agency for Health Care Policy and Research Publication Nos. 93-0050 and 93-0051.
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- Ketter, T. A., et al: The emerging role of cytochrome P450 3A in psychopharmacology. *J Clin Psychopharmacology*. 1995;15:387-398.
- Nemeroff, C.B., et al: Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry* 1996; 153:311-320.

Preskorn, S.H., et al.: Somatic therapy for major depressive disorder: selection of an antidepressant. *J Clin Psychiatry* 53:9 (suppl): 5, 1992.

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TABLE 1

Agent*	Reported Advantages	Potential Disadvantages
Sertraline (Zoloft)	Intermediate half-life - once/daily dosing Linear kinetics Minimal age effects on clearance Non-anticholinergic No sign. effect on cardiac conduction, BP	Moderate effects on P-450 2D6 hepatic isoenzyme -- drug interaction risk
Paroxetine (Paxil)	Intermediate half-life - once/daily dosing Fewer GI adverse effects reported No sign. effect on cardiac conduction, BP	Anticholinergic Non-linear kinetics Age effects on clearance Potent effects on P-450 2D6 -- drug interaction risk
Venlafaxine (Effexor)	Minimal effects on hepatic P-450 system	Short-half life (twice/day dosing required) Hypertensive in older patients in higher doses Prominent nausea Modestly increases serum cholesterol
Nefazodone (Serzone)	Sedating Non-anticholinergic No sign. effect on cardiac conduction Infrequent sexual dysfunction	Short-half life (twice/day dosing required) Non-linear kinetics Potent effects on P-450 3A3/4 -- drug interaction risk Mildly hypotensive
Bupropion (Wellbutrin)	Non-anticholinergic No sign. effects on cardiac conduction, EF, BP Infrequent sexual dysfunction	Short-half life (twice/day dosing required) Risk of seizures, especially at higher doses Restlessness can occur
Nortriptyline (Pamelor)	Established efficacy in severe depression Defined optimal plasma concentrations (50-150 ng/ml)	Anticholinergic Orthostatic hypotension <b>Contraindicated in presence of cardiac conduction delay</b>

\* Fluoxetine (Prozac) excluded due to its prolonged elimination half-life

**TABLE 2**

<b>Agent</b>	<b>Starting Dose mg/day</b>	<b>Maximum Dose mg/day</b>
Nortriptyline (Pamelor)	25	100
Sertraline (Zoloft)	50	200
Paroxetine (Paxil)	10	50
Venlafaxine (Effexor)	75	225
Nefazodone (Serzone)	50	600
Bupropion (Wellbutrin)	75	450