# Clinical Management—Imipramine / Placebo Administration Manual

## NIMH Treatment of Depression Collaborative Research Program

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# Introduction

The Clinical Management—Imipramine / Placebo Administration Manual was written in response to a request from the NIMH Treatment of Depression Collaborative Research Program to develop a standard procedure for the administration of the imipramine and placebo conditions in the Program. The manual was originally prepared in 1979 under an NIMH Professional Services Contract and has gone through several revisions, first in response to suggestions of the staff and the Advisory Group of the Program, and subsequently to improve the clarity of the Manual, until its final revision in 1986. The major impetus for development of the Manual was the fact that the two psychotherapies in the study each had extensive manuals outlining standards for their administration. These manuals could be used for training therapists and for assessing their performance in order to maintain quality and consistency of the treatments. Since the imipramine treatment condition would provide standard reference data against which the psychotherapies were to be measured, it was important that the pharmacologic conditions be administered in such a way as to achieve quality and consistency of pharmacotherapists' performance, and to assure maximum patient compliance and minimum dropout rate. The guidelines regarding therapists' behavior were aimed at attaining maximum effectiveness of the treatment while avoiding contamination with the specific psychotherapeutic approaches being studied. The Manual also contains the dosage schedule for the imipramine and placebo conditions, in order to guarantee that a sufficient dosage of medication is given to each patient assigned to the imipramine condition in the study.

The Manual thus attempts to address two major goals. The first goal is related to the design of this particular study, and involves proper dosage schedule, avoidance of contamination of the pharmacologic treatment condition by various psychotherapeutic techniques, etc. The second goal is to set standards for the effective administration of medication in an outpatient setting, taking into account the factors deemed important in the successful maintenance of compliance (e.g., conveyance of interest in the patient and skillful management of side effects) in order to provide the maximum opportunity for the treatment condition to be of help to the individual patient. The first goal is study related only, while the second goal relates to both the successful completion of the study and to the question of more general standards for the successful delivery by a physician of medication in an outpatient setting.

The values in this manual which relate to the successful treatment of patients with medication are those of the authors based on their clinical experience in the use of psychopharmacology. These values have not been validated in any specific way, but simply form a set of standards, much as those embodied in the psychotherapies, that are believed to be important on the basis of clinical practice experience. It is hoped that the manual will be read with its dual purpose in mind and that readers will find various aspects useful whether their interest is in the adaptation of the manual to a research study or in teaching the fine art of clinical management for the successful administration of medication to patients.

## I. Purpose of Study

The major aim of the study for which this manual has been generated is to evaluate the effectiveness of two promising short-term psychotherapeutic approaches, Cognitive Behavioral Therapy and Interpersonal Psychotherapy, for treating nonbipolar, nonpsychotic outpatient depressive illness. The effectiveness of the psychotherapies will be assessed by comparing them to a treatment that has been demonstrated to be effective for this population, specifically a tricyclic antidepressant medication (imipramine). A double-blind placebo condition is included in the design, primarily to establish the adequacy of the imipramine condition as an efficacious reference treatment in this study. Both active medication (imipramine) and pill placebo are provided in the context of the Clinical Management—Imipramine / Placebo Condition (CMIPC) developed specifically for this study.

## II. Aims of the CMIPC

### A. General Aims

In order to provide valid data with which to compare the effectiveness of the treatments and with which to address other major questions posed by this study, each of the study treatment conditions must be provided in an optimal fashion allowing for maximal therapeutic effectiveness. The purpose of this manual is to describe the Clinical Management Condition and to outline the procedures involved in the optimal delivery of this condition. The CMIPC has been designed to resemble as closely as possible the manner in which medications would be most effectively administered in the clinical management of depressed outpatients. Moreover, the interpersonal transactions of the pharmacotherapist and patient have been defined so that the CMIPC will minimally overlap with the psychotherapy conditions.

### B. Specific Aims

One of the main goals of the CMIPC is to foster and maintain the kind of therapeutic relationship between patient and pharmacotherapist that will promote compliance with the treatment regimen in general and, in particular, compliance with medication. A second major goal of the CMIPC is to promote the patient's continuation in the study throughout the entire 16-week study period. This will be most difficult to achieve both early and late in treatment: early if the patient is not receiving obvious benefit; later if the patient has a partial or complete therapeutic response and does not appreciate the need to continue therapy. Maintaining a very low attrition rate is crucial in producing reliable data. A third major goal is the effective use of pharmacotherapy to provide an adequate reference condition to which the other treatment conditions can be compared. The goal involves removal of depressive target symptoms presented by the patient, producing a state of remission.

## III. Protocol for the CMIPC

### A. General Organization and Focus of the Psychopharmacotherapy Sessions

The pharmacotherapist must be responsive to the patient's complaints and needs while also maintaining control in the interview. This can best be accomplished through a rational and organized structuring of sessions. The pharmacotherapist's ability to focus and appropriately sequence the inquiry and discussion is of great importance for an effective psychopharmacotherapy session. In considering the issue of initial focusing, it is important to remember that the patient is finally entering a treatment situation after several weeks of preliminary screening and data gathering. The patient's clinical needs and treatment expectations are of the highest priority and deserve the utmost respect and attention as the pharmacotherapist proceeds with organizing the interview. The initial sessions should ideally be developed as therapist–patient collaborative efforts to *characterize general and specific features of the depressive episode.* A therapeutic agenda can thus be established on which to base treatment expectations consistent with the psychopharmacotherapy approach.

The appropriate organization and structuring of the CMIPC sessions together with the inclusion of the appropriate content should sufficiently distinguish the sessions from psychotherapy and help prevent the pharmacotherapist from straying into "psychotherapeutic territory." We do not wish to encourage an

interview structure or process so rigidly structured as to preclude opportunities for *empathy, support*, and those *naturally spontaneous* and more casual exchanges that permit treatment to be carried out in a *warm* and *truly human way.* However, open-ended inquiry into or discussion of interpersonal relationships is to be especially avoided.

The appropriate *sequencing* of clinical inquiry and therapeutic discussion is also an important factor influencing the effectiveness of the session. Among the more frequent examples of inappropriate sequencing are the discussion of medication effects *prior* to the elicitation of target symptoms and the premature discussion of side effects prior to a thorough discussion of therapeutic benefits of the medication.

### B. Initial Session

The initial patient visit will consist of a 45-minute to 1-hour session. During this session the pharmacotherapist will attempt to establish a positive relationship with the patient in the context of a thorough discussion of the course of the present as well as previous episodes of depressive illness. The elucidation of the past history, family history, and relevant medical history will focus on elaborating information about clinical symptoms of major depression.

Considerable attention will be devoted to the establishment of the *target symptoms** as a basis for ongoing clinical assessment and management within CMIPC. The content of subsequent sessions will depend on the accurate and comprehensive establishment of target symptoms in the initial session. In addition to providing material for future sessions, discussion of target symptoms will help structure sessions so that active psychotherapeutic interventions can be avoided, thus keeping the pharmacotherapy sessions as free from "psychotherapeutic contamination" as possible. The initial comprehensive determination of target and accessory symptoms will also be necessary for later detection of study medication side effects.† The *Symptom, Sign, Side-Effect Checklist* (*see* Appendix 1) will provide a basic inventory and format for obtaining the baseline and subsequent medication side-effect assessments. Also, in the process of assessing the patient's symptoms and experience of depressive illness, the pharmacotherapist should routinely and completely assess suicidal ideation and impulses. This will be particularly crucial in patients with a previous history of depressive illness involving suicidal ideation or behavior.

A basic and easily understandable explanatory model of how and why antidepressant medication is effective should be provided. Theoretical and practical aspects of the treatment rationale should be presented in the patient's own language, and discussion of the patient's concerns and questions should be actively facilitated.

The rationale for the use of medication in the treatment of depression should be explained and any resistance to the idea of medication therapy should be addressed. The patient should be allowed and even encouraged to express his or her concerns, fears, and attitudes regarding medication in general and psychotropic drugs in particular. The interpersonal ambience should provide the patient an opportunity to air prejudices, distortions, and fantasies regarding either the positive or negative effects of the medication. These distortions should be corrected by responding to the patient's questions with further clarification and support.

It is critically important to obtain a comprehensive history of previous experiences with and responses to pharmacotherapy (including specific medication dosages and the duration of treatment) *prior* to explanation and discussion of the current treatment. Educating the patient about the individual variability of responses often encountered with different antidepressants, coupled with assurances that medication response will be closely monitored, will help the patient overcome possible negative attitudes based on previous experiences and/or ignorance or misinformation about antidepressant pharmacotherapy.

The patient should be instructed about the importance of taking the prescribed dosage of study medication and apprised of the fact that adjustment of the dosage may be necessary to achieve the desired effect. The patient should also be instructed that it may be 2 to 6 weeks before a therapeutic response is achieved and should be informed about which symptoms (e.g., sleep disturbance, appetite disturbance) are likely to respond to treatment initially. The concept of *gradual response* or *progressive improvement* should be discussed so that patients do not unrealistically expect an early "all or none" response.

*Target symptoms include sleep disturbance, appetite disturbance, diurnal mood variations, anhedonia, feelings of hopelessness, suicidal ideation, etc. Symptoms such as anxiety, irritability, and hypochondriacal preoccupations should also be explored.

†The term "study medication" will be used throughout the CMIPC as a generic term for the active drug or placebo without implying one or the other drug possibility.

The possibility of the occurrence of side effects during treatment should be discussed. Pharmacotherapists should mention the side effects which most frequently occur during treatment (dry mouth, dizziness or lightheadedness, especially on changing position, blurred vision, nonspecific sedative effects, and delayed micturition). The patient should be instructed that these side effects are not dangerous if reported to the pharmacotherapist and managed correctly. If mild side effects do occur, the patient will be instructed to continue the medication at the prescribed dose, if possible, until the physician can be reached. If more severe side effects occur and the patient is not able to reach the pharmacotherapist immediately, the medication should be temporarily discontinued until the therapist is contacted.

It should be emphasized that the treatment is based on *specific* therapeutic effect and that the medication is not a nonspecific sedative or tranquilizer. It should also be made clear that the *medication is not addicting* and that, although the rationale for its use may not be understood by many lay people, its use is grounded in scientific evidence that certain types of depression may require pharmacological intervention to treat an underlying physiological disturbance. The patient should be instructed that the treatment being prescribed is expected to help in a high percentage of depressed patients but that the treatment will be reevaluated should any sustained worsening of depressive symptoms occur. The patient should be advised that other medications (e.g., tranquilizers and sedatives, proprietary medications, hormone supplements, excessive caffeine, excessive alcohol, etc.) should not be ingested during the course of treatment.

The patient should be instructed that future visits will be confined to 20- to 30-minute sessions devoted to reviewing the patient's general progress, the current status of depressive signs and symptoms, and possible side effects, as well as to discussing his or her questions and concerns. It should be made clear that this time limit is relatively inflexible and will not be modified unless there is some pressing need. The patient should be instructed that these sessions will be conducted on a weekly basis but that in case of severe side effects or worsening symptoms of the illness, it will be possible to reach the pharmacotherapist or an associate by telephone.

Especially during the initial session, the pharmacotherapist should attempt to develop an accepting, understanding, and supportive relationship with the patient and to convey hope and optimism regarding the outcome of treatment. The pharmacotherapist should also clearly communicate an expectation that the patient will improve and should explicitly link this expectation of improvement or mitigation of target symptoms with the idea of positive therapeutic outcome as a result of antidepressant pharmacotherapy. By assisting the patient in developing a positive set of hopeful expectations linking the relief of core symptoms with medication effects, the pharmacotherapist creates opportunities for ongoing therapeutic discussions focused on those aspects of the medical treatment of depressive illness that are personally important to the patient.

Here we would like to present a brief sketch of an ideal first session. In such an idealized version of the initial psychopharmacotherapy session, we see the pharmacotherapist warmly greeting and welcoming the patient, and providing an explicit introduction that unambiguously establishes his/her role as the doctor who will be in charge of the patient's clinical care for the duration of the study. This introduction should distinguish the pharmacotherapist's role as primary managing clinician from the research roles of various study personnel the patient has previously seen. It is during the initial exchange that the pharmacotherapist clearly establishes the overall importance of the patient's clinical care and well-being in the study context. The psychiatrist should also demonstrate knowledge about the study in general.

After acknowledging review of the patient's diagnostic summary, the psychiatrist should begin an independent evaluation with the primary objective of establishing a set of *core or target symptoms*, manifestations of the underlying disease process which will serve as indicators of potential response to the treatment that will be prescribed. Accessory signs and symptoms can be simultaneously elicited. Screening for the presence of possible medication side effects at baseline can also be done as an associated component of this phase of the session; however, the use of the Symptom, Sign, Side-Effect Checklist as a primary device or method to maintain structure is definitely not recommended. At appropriate junctures, clinical attention and questions should be directed towards life problems with the objective of information gathering, learning about the patient as a person, and conveying empathic concern. The pharmacotherapist should not, however, engage in psychodynamic incursions and digressions that not only violate study protocol but may also be "antitherapeutic," given the parameters of the pharmacotherapy condition.

We recommend that all of the above be completed in approximately the first 30 minutes of the initial session so that at least 15 to 30 minutes are available for the psychiatrist to establish and convey a sense of

authoritative responsibility and knowledgeability about the pharmacotherapy, to appropriately educate the patient about how and why the medication can help, and to allow for questions from the patient and further discussion.

### C. Second and Subsequent Sessions

At the second and subsequent sessions, the pharmacotherapist will meet with the patient for approximately 20 to 30 minutes. A systematic inquiry into the presence, intensity, and features of the already established target symptoms that characterize the patient's depression should provide the basis for the assessment of response to treatment. This systematic inquiry should also provide the framework for ongoing assessment during subsequent sessions. Similarly, a systematic evaluation for side effects will be made during the second and all subsequent sessions.

The *Symptom, Sign, Side-Effect Checklist* will serve as a standard format for evaluating the above. Regarding technique when administering the *Symptom, Sign, Side-Effect Checklist,* we suggest that the pharmacotherapist inquire about the presence of items by presenting them in groups of related items, e.g., "Have you ever had weakness, faintness, dizziness, lightheadedness, headaches, visual disturbances?" This allows the screening for symptoms and signs to be done efficiently, leaving more time for other therapeutic tasks. Sitting and standing blood pressures should be routinely taken during the first, second, fourth, and eighth sessions to assess for postural hypotension. If at any other time the patient presents with signs or symptoms suggestive of postural hypotension (i.e., dizziness or lightheadedness upon arising from a sitting or recumbent position), then the sitting and standing blood pressure should be taken, recorded, and appropriate clinical management initiated.

During the second session the patient will be asked about reactions to the medication, possible side effects, and possible early therapeutic effects. Patients who are unusually sensitive to the medication or who have idiosyncratic reactions (palpitations, etc.) will be identified at this time.

Since it is highly possible that no therapeutic response will have occurred by the second session, special effort will usually be necessary to reinforce the patient's continued hope and optimism regarding improvement. The patient should be encouraged to continue the medication and should also be instructed that higher doses usually produce symptomatic improvement. Although it is unlikely that the patient will have any appreciable side effects to the medication at this point, there may be minor side effects, especially in patients who are apprehensive about taking medication. Further educative efforts regarding the "hows" and "whys" of antidepressant medication may be helpful and perhaps necessary to avoid dropouts and/or noncompliance during the early stages of the pharmacotherapeutic treatment.

Here, we would like to emphasize the importance of flexibility in determining the duration of pharmacotherapy sessions. For some patients whose clinical course has demonstrated significant improvement, a 20-minute visit may be quite adequate and appropriate. On the other hand, we do not recommend visits under 15 minutes or over 30 minutes, except in extraordinary circumstances when the clinical management definitely requires an extended period of time.

### D. Prescription of Study Medication

Study medication will be prescribed each week and will consist of identical containers of identical capsules for both the imipramine and the placebo condition. A sufficient number of capsules should be provided to cover the possibility of a missed appointment by the patient or pharmacotherapist, i.e., an additional 2 to 3 days of study medication may be prescribed. However, medication may only be prescribed for a maximum period of 10 days or 40 capsules (2000 mg), whichever is less. If there is risk of an overdose, the pharmacotherapist may choose to have the patient return for an additional appointment that week in order to limit the total amount of medication the patient has in his/her possession at any one time. Patients are instructed to return all unused medication to the therapist at each session. The physician must maintain an accurate record of all unused study medication. The number of capsules prescribed and the number of unused capsules should be recorded at each session.

The CMIPC dosage schedule is designed to optimize the possibility of a full response to the study medication by approximating usual clinical practice. To accomplish this, an attempt should be made to systematically expose each patient to 200 mg of study medication by the third week of the study and to maintain a minimum dosage of 200 mg of study medication for a period of at least 4 weeks. If, at any dosage, the patient manifests severe side effects which appear to be dose related (e.g., anticholinergic effects, drowsiness), this may signify that a lower dose is the maximum tolerated dose at that time. If the patient does not appear to be responding optimally to the study medication at a given dosage level, the dosage may be increased up to the ceiling of 300 mg. This potential

range of dosage combined with flexibility in the dosage schedule should assure an adequate trial of medication for each patient (*see* Appendix 2).

The very first dosages taken by the patient should constitute a test for hypersensitivity to imipramine. If overwhelmingly severe side effects (e.g., extreme dysphoria or anxiety, massive sedation, headache) emerge in response to the initial dosage of the medication, the dose may be dropped to 25 mg. However, if the patient is not able to achieve a dosage of 50 mg without significant or severe side effects, he/she should then be considered hypersensitive to the medication and withdrawn according to the study guidelines.

If moderately severe side effects emerge as the dose is being increased, the patient should attempt to contact the pharmacotherapist. Several alternatives are then available. For example, the dosage may be redistributed over the course of the day in an attempt to increase patient tolerance, or the dosage may be temporarily reduced in order to allow the patient to accommodate. If dosage has been decreased because of side effects, the pharmacotherapist should later attempt to increase the dosage more gradually until a therapeutic level has been achieved unless there is a resurgence of severe side effects, the appearance of new and serious side effects, or clinical deterioration. Over the ensuing weeks, the pharmacotherapist may increase the medication up to the maximum dosage of 300 mg, based on the patient's response to treatment.

The study medication should be maintained at the maximum tolerated dose for *at the very least* 4 weeks. At that time the pharmacotherapist may initiate a gradual decrease at a rate *not to exceed 50 mg per week* to maintenance dosage (usually one half to two thirds of the maximum tolerated dosage). Decrease in medication to a maintenance level should be based on the psychiatrist's evaluation of the patient's clinical condition and response to medication. Some patients may require the full therapeutic dose as maintenance. However, not all patients may be able to tolerate 200 to 300 mg daily of study medication. If only lower doses are tolerated, therapists should note the reason for this and use direct patient quotations when possible. *Under no circumstances should patients be prescribed less than 100 mg per day of study medication*. In the rare case where a patient cannot tolerate at least 100 mg of study medication, the patient should be withdrawn from the study and an appropriate referral should be made. If a patient misses a dose of medication, it should be recorded and the patient advised not to make up the missed dose, but to continue with the prescribed dosage schedule.

We would like to emphasize the importance of dosage flexibility. The schedule guidelines recommended here are not meant to be absolute, although there is, indeed, an upper limit of 300 mg of study medication which is not to be exceeded. Some patients, because of unusual sensitivity to the medication, may need to be advanced more slowly than suggested. In these cases, the pharmacotherapist may adopt a scheduling strategy of alternating doses every other day to achieve a more gradual dosage increase. Dosage changes and titrations are also recommended to manage side effects, although the therapist should, if possible, attempt to deliver the maximal therapeutic dose. In addition, dosage flexibility is also recommended during the latter weeks of treatment as patients may experience relapse when a decrease in dosage occurs. In such circumstances we recommend that the patient continue on sufficient medication to maintain the therapeutic response.

### E. Pharmacotherapy Management Issues

*Drug interaction with other medication.* Patients should be instructed to avoid all other medications, including over-the-counter compounds, if possible, during the study treatment. The use of proprietary (nonprescription) medication that the patient may take under ordinary circumstances such as aspirin or acetaminophen for headache or laxatives for constipation is acceptable, but the use of prescription medication is *not* allowed. If the patient is using other medication (e.g., laxatives), he/she should be advised to allow at least a 2-hour interval between the time of ingesting study medication and the time of ingesting the laxative to avoid possible interference with absorption of the study medication. If the ingestion of a prescription medication is unavoidable (e.g., antibiotic for an acute febrile bacterial illness), the medication, dose, and reason for prescribing should be recorded. Patients should also be told that if they require dental work while on study medication, their dentist should be advised that they might be on a tricyclic medication that could interact adversely with the epinephrine-like medications often used in local anesthetic preparations.

*Laboratory work.* At any time during the course of treatment, the CMIPC psychiatrist may request laboratory tests (e.g., liver function tests) or an evaluation of the patient by the medical evaluator.

*Side effects management.* The thorough discussion and successful management of disconcerting or troublesome side effects early on in the course of treatment is often of critical significance with regard to

pharmacotherapy compliance in general. Detecting anxiety associated with an increase in dosage or disturbing side effects resulting from such an increase is necessary for the successful management of further dosage adjustments. Mild side effects may often be adequately managed by explaining to patients that the severity of side effects usually decreases over time. This is most effectively accomplished through discussion carried out in the context of a concerned, reassuring, and supportive attitude on the part of the pharmacotherapist. Moderately severe side effects are usually best managed by a temporary lowering of the dose. Advice may be given regarding physiological management of side effects (e.g., laxative diet for the mitigation of constipation). Managing more severe side effects may require a permanent lowering of the dosage. Other than the ordinary use of proprietary medication, adjunctive medication for the management of side effects (e.g., urecholine for the management of urinary retention) is not permitted.

### F. General Management Issues

*Avoiding dropouts.* The avoidance of dropouts from the clinical management condition will depend to a great extent on the nature of the relationship established between the pharmacotherapist and patient. In order to avoid dropouts, it is important that the pharmacotherapist not only be supportive and encouraging, but remind the patient of the delayed effect of the medication and reiterate the possibility that the dosage may need to be increased. Without such attention and reassurance there is a danger that the patient who experiences an absence of therapeutic benefit particularly in the presence of side effects may discontinue treatment within the first 2 to 4 weeks.

*Phone calls.* Especially during the early weeks of treatment, the physician must be available to the patient for telephone calls between appointments for questions about side effects which may occur as medication dosage is increased. Phone calls allow the pharmacotherapist to receive clinical information from the patient about symptoms or medication side effects, make a determination about their significance, and provide an opportunity for immediate management of problems. In addition, they provide the patient with the reassuring knowledge that a concerned and available physician is managing the psychopharmacotherapy. The reassurance provided by such brief calls in everyday clinical practice often makes the difference between a successful outcome and early treatment dropout of a patient who might have responded to the medication. These phone calls can often provide the support necessary to assist the patient in continuing medication despite depressive feelings of hopelessness and discouragement or fears and anxieties stimulated by the occurrence of side effects. It is often reassuring to a patient to know that the physician will be available at a particular time of day to respond to phone calls if necessary. The patient should also be instructed that in the event the pharmacotherapist is not immediately available, there is an emergency number at which to contact a psychiatrist 24 hours a day. In addition, at the outset of the study, each patient is provided with emergency numbers for contacting the Principal Investigator and Project Coordinator at that site. *Phone calls are not to constitute supplementary or adjunctive therapy.* The CMIPC physician should keep an accurate record of every phone call received from the patient and his/her family. This information should be noted and should include date, time, length of call, content of call, specific and general concerns, and the therapist's response (e.g., advice, instructions, education, and medication adjustments).

*Family assessory visits.* When absolutely necessary to prevent patient dropout or provide reassurance, brief accessory visits with a patient's family members may be scheduled. On the rare occasion that such sessions are necessary, they should be brief and should provide information about the nature of the depressive syndrome and education regarding the pharmacotherapy. Such intervention may result in increased family support which may be helpful and at times necessary in order for the patient to endure the frustrations of waiting for a pharmacotherapeutic response. Family therapy intervention of any form is *not* to be conducted.

*Clinical deterioration.* A clinical management issue of major significance is the referral of unimproved or deteriorating patients for a clinical evaluation. If the patient has shown no improvement or begins to show clinical deterioration after a reasonable therapeutic trial of study medication and further continuation under such circumstance would be detrimental to the patient, a referral should be made for a clinical evaluation to determine whether the patient should be withdrawn from the study. If the patient is withdrawn from the study, appropriate referral arrangements will be made by research staff. The pharmacotherapist has full responsibility and authority to refer the patient for clinical evaluation at any time regarding the patient's suitability for remaining in the study.

### G. Termination

Even though active psychotherapy as such is not provided in the CMIPC, a significant doctor–patient

relationship will likely develop during the 16 weeks of the study. In light of this, discussion of termination should occur and will likely be an important issue in the last several sessions. A sensitively directed inquiry and guided discussion that permits the patient to express feelings and ideas about having participated in the study, attitude towards the therapist, fears about discontinuing medication, future plans, and possible future therapy needs is essential. Deficiencies in dealing with termination issues can lead to instances of "acting out" (e.g., patients abruptly and unilaterally stopping their medications or not returning for tapering sessions). If previously unrecognized or currently unresolved termination issues still remain, an additional session during the tapering phase may be necessary to discuss such issues. However, this is not encouraged as termination issues should be adequately addressed during the final sessions.

If, at any time during the course of treatment, the patient inquires about continuing treatment beyond the 16-week study period, he/she should be reassured that an appropriate referral will be made if it appears that the patient needs further treatment at the conclusion of the study period.

## IV. Maintenance Phase

### A. Medication Schedule

In most cases, patients who demonstrate a "medication response" will do so between the second and eighth week of treatment. The period after the demonstrated therapeutic response should be considered the maintenance phase. After the patient has shown such a response and has been maintained on the maximum tolerated dosage for at least 4 weeks, the pharmacotherapist should gradually adjust the dose of medication to a maintenance level of one-half to two-thirds of the therapeutic dosage. This should not be attempted until it is clear that clinical improvement is enduring, not transient, and that the therapeutic response is maximal, producing a definite decrease or complete absence of target symptoms. Premature reduction or discontinuation of medication can lead to relapse in a high percent of cases. For the purpose of this study, maintenance dosage should be no lower than 100 mg per day. Therefore, patients in the pharmacotherapy condition should continue to receive *at least* 100 mg of study medication even after the initial phases of the study treatment period. *Care must be taken to maintain the medication dosage at a sufficient level to maintain a maximal response.*

It is crucial that the patient who is showing a medication response as evidenced by clinical improvement be educated regarding the need to continue medication throughout the entire study period. This should be emphasized especially at the point when the patient begins to show improvement as patients are at high risk for discontinuing treatment shortly after an initial improvement.

In the event that a patient shows a dramatic improvement and develops a state of euphoria or hypomania, it may be necessary to lower the dosage. If this occurs, the therapist should attempt to maintain at least the minimum medication dosage of 100 mg. If the episode progresses to definite mania, it may be necessary to discontinue medication and to withdraw this patient from the study.

### B. Evaluation of Response to Treatment

*The Symptom, Sign, Side-Effect Checklist* will serve as a standard format for assessing symptoms as well as evaluating side effects, and will be completed after every session. Change in the number and intensity of target symptoms of depression and the presence and severity of side effects should be the primary referents for making decisions concerning changes in medication dosage. It is important that increases in the medication dosage be continued as long as any target symptoms of depression remain, since patients who achieve only partial improvement frequently relapse on medication several weeks later.

In the case of patients who fail to improve, the pharmacotherapist and/or the patient may assume that the patient has been receiving a placebo. However, it is important *not* to make this assumption as some patients may respond slowly, not showing a clinical response until exposed to an adequate blood level for several weeks (blood levels will be determined throughout the study, but will *not* be available to the clinicians for dosage adjustments). For this reason, it is essential to continue to increase the medication dosage if possible even though improvement has not been achieved. Since an adequate dose may make the difference in response, it is entirely reasonable and honest to encourage a patient to continue treatment with the expectation of a possible future therapeutic response. In summary, pharmacotherapists should manage medication "as if" every patient were receiving active medication.

## V. The Interpersonal Context

### A. Therapist Factors

*Psychopharmacologic experience.* It is essential that pharmacotherapists have sufficient experience with the use of imipramine to have an appreciation for the importance of adequate dosage as a condition for maximal therapeutic response. They should also be aware of the relationship of imipramine blood levels to therapeutic efficacy (e.g., both the unpredictable relationship between the dosage prescribed and actual blood level of imipramine attained in individual patients, and the concept of delayed therapeutic response and its relationship to adequate dosage). Pharmacotherapists should also be familiar with the relative medical importance of imipramine side effects and methods for their management. A background of knowledge about, and clinical experience in, the use of tricyclic antidepressants coupled with confidence in their therapeutic value will help foster a therapeutic relationship that can facilitate patient compliance, prevent premature discontinuation of medication, and contribute to a beneficial outcome.

The importance of this knowledge is highlighted by a recent study of the treatment-resistant depressions. In examining the reasons for patients' failure to respond to pharmacotherapy combined with supportive psychotherapy, researchers found that at least 50 percent of the patients did not receive an adequate trial of any tricyclic antidepressant medication because the physician did not prescribe adequate doses of the medication or stopped the medication prematurely due to patient noncompliance or the emergence of side effects of little medical consequence. Furthermore, noncompliance was often a result of lack of an adequate relationship with the physician. For some patients, failure to comply with the treatment regimen was attributed to insufficient information about side effects or about the course of therapeutic effect.

### B. Role of Therapist

Of critical importance is the pharmacotherapist's role as physician with primary clinical responsibility for the patient. The pharmacotherapist should function as the patient's physician just as a physician would in a nonresearch clinical setting. Pharmacotherapists should not permit the study design, research procedures, or their role as members of a research team to interfere with their role of primary responsibility for the care of the patient. Pharmacotherapists should actively assure the patient of their primary and unwavering commitment to the patient's care. The supportive and therapeutic engagement of the patient is an integral component of the CMIPC. In order to engage the patient rapidly in a positive relationship and inspire confidence in the treatment condition, pharmacotherapists should create an ambience of warmth and trust and convey a positive and optimistic attitude about the patient's clinical treatment. Ideally pharmacotherapists should be able to communicate relevant clinical information to the patient in understandable terms, if possible in the patient's own words, and convey their knowledge and experience in the pharmacotherapy of depressive disorders.

Any tendency to administer the pharmacotherapy condition mechanically, to maintain inappropriate distance, or to relate in a perfunctory way is antitherapeutic and must be avoided. The rationalization of antitherapeutic behavior such as distancing by conceptualizing it as consistent with the role of "research therapist" should be considered a breach of doctor–patient responsibility. Neither remoteness nor aloofness in the name of therapeutic neutrality has a place in the CMIPC. It is hoped that the pharmacotherapy condition in this study will approximate the best and most effective treatment that could be provided by an eclectic psychiatrist, given the study constraints on active psychotherapeutic intervention.

### C. Interpersonal Processes

Since one purpose of this study is to examine differential treatment effects, it is important to maintain specific treatment approaches as purely as possible while at the same time assuring the maximum possible therapeutic effect within each condition of the study. The study design can no more tolerate the "bootlegging" of active psychotherapy into the pharmacotherapy condition than it would tolerate the "bootlegging" of active medication into the psychotherapy conditions.

In order to avoid potential overlap between the CMIPC intervention and processes and the two psychotherapy interventions, it is necessary to specify the permitted and desirable elements of the interpersonal process in the pharmacotherapy condition as well as those which are prohibited.

Although pharmacotherapists should concentrate on target symptoms and side effects, certain interpersonal processes are both permitted and suggested in the CMIPC conditions. Clinical management requires the basic keen observational skills, interpersonal sensitivities, and technical interventions that are ideally characteristic of any competent psychiatrist.

The pharmacotherapist should engage in the types of interpersonal interventions which foster a good doctor–patient relationship, while at the same time avoiding specific interpersonal interactions that would be characterized as formal psychotherapeutic interventions. For example, inquiry into the cognitive, affective, and behavioral–interpersonal realm for the purpose of clarifying the patient's current state or situation is permitted and can be successfully accomplished without utilizing a dynamic, cognitive, behavioral, or other specific organized, systematized psychotherapeutic approach. The separation of these two levels of inquiry and intervention is somewhat arbitrary and may be experienced by the pharmacotherapist as a constraint.

However, it is important that the prohibition on active psychotherapeutic intervention not result in the patient's receiving limited emotional support. The general injunction against "active psychotherapy" should not lead to self-consciousness or rigidity that diminishes the therapist's responsiveness to the patient's immediate need for supportive interaction. In summary, *clinically indicated and appropriate supportive psychotherapeutic measures and interventions are sanctioned, whereas interventions related to specific organized systems of psychotherapy are not permitted.*

The following sections define several areas of interpersonal process and types of intervention that *are* permitted within the context of the Clinical Management Condition and several that are not.

1. *Interpersonal context factors.* Depression is an illness in which the patient is frequently anxious and may have negative expectations regarding the treatment intervention and outcome. Because of this, it is critically important to elicit the patient's confidence in the treatment. This can be accomplished through attention to the *interpersonal context* of the treatment. Research has shown that medication is more efficacious when it is administered within a supportive interpersonal context. Frequently, the patient will need reassurance to continue to take medication in spite of mild and medically insignificant but anxiety-provoking side effects such as dry mouth and blurred vision. The patient may also need support in the face of criticism by family, friends, or peers who communicate negative attitudes about the medication. The patient's positive and meaningful relationship with the physician is crucial in sustaining medication compliance under adverse or unsupportive psychosocial circumstances. If the patient has trust in the physician, believes in his/her knowledge and competence, and maintains a conviction that the medication will be helpful, the patient will persist in the course of therapy even in the absence of initial improvement.

2. *Psychological support.* Psychological support should be provided by the pharmacotherapist throughout the course of treatment. Conveying a sense of hope and optimism is especially necessary in the earlier phase of treatment when the patient is likely to develop doubts that the treatment will help in the face of an initial lack of improvement. Reassurance may be particularly important if the patient is having medication side effects or physical symptoms of depressive illness. Furthermore, the patient may need special reassurance in the face of criticism of medication use by relatives or friends.

3. *Instruction, education, and information giving.* It is particularly important that, in the first session, the patient be instructed about the characteristics of the medication and the reason that it is given for depression. In addition, there should be some discussion of the notion that depression may be related to a change in brain biochemistry which the medication may help correct. This explanation must be general enough to allow for the possibility that psychotherapeutic treatment can also be effective and the possibility that the type of medication used in the study may not be effective for each individual patient. Physical symptoms of depression and the side effects of the medication should also be discussed.

4. *Advice.* Frequently, patients will ask what they can do to help themselves out of their depression. The pharmacotherapist might give simple suggestions to the patient such as advising increased physical activity (e.g., age-appropriate exercise). Patients may also request advice concerning whether to make decisions or to attempt to engage in certain activities during a depressive episode. Simple advice is permitted within the context of the CMIPC. For instance, a patient under certain circumstances might be advised to avoid a particular stressful situation or advised to socialize more, depending on the situation. Pharmacotherapists should keep notes on any such direct advice that is given.

5. *Ventilation and abreaction.* Patients will usually need to describe their depressive feelings at length and share their fears and doubts. Within the limited timeframe of the CMIPC sessions, patients should be permitted to do this to the extent that it is thought to be of help in sustaining a positive therapeutic relationship.

The following list defines several areas of interpersonal processes and types of intervention which are *not* permitted within the context of the CMIPC:

1. *Focusing on specific psychological themes,* especially interpersonal relationships and cognitive distortions.
2. *The interpretation* of interpersonal events, styles of interpersonal relating, suppressed feelings, or distorted cognitions.
3. *Interpretations* relating to recent losses, secondary gain, and other psychological mechanisms.
4. *Clarification of the patient's feelings* toward others or toward the therapist.
5. *Specific behavioral instructions or routines* other than simple advice about activity such as instructions that the patient should be going out more as he/she shows improvement.
6. *Explanations of the psychodynamics of depressive conditions* (e.g., suppressed anger, shame, and helplessness).
7. *Any involved interpersonal interaction.*

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