

**TREATMENT FOR ADOLESCENTS WITH DEPRESSION STUDY (TADS)
PHARMACOTHERAPY TREATMENT MANUAL**

Final Version (5.1)

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Adapted from the Treatment of Pediatric OCD and Multimodal Treatment of Children With
ADHD Pharmacotherapy Manuals

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1.0 Overview

1.1 Background and Rationale:

This Pharmacotherapy Treatment Manual (PTM) addresses two general areas: research and clinical practice. In the research area, its goal is to clearly outline procedures and practices that can and will be carried out similarly at each research site to ensure maximum effectiveness of pharmacological treatment without contamination with other treatment approaches. In the clinical practice area, the goal is to set standards for most effective administration of medication in an outpatient setting for patients with MDD. This manual provides clear guidelines for clinical treatment and facilitates comparability and fidelity of treatment across research sites. The philosophy/strategies in this manual are based on extensive experience using medication strategies in clinical trials in pediatric and adult MDD and other neuropsychiatric disorders in patients and adolescents.

1.2 Aims of the Study:

The major aim of the study—for which this Pharmacotherapy Treatment Manual (PTM) has been generated—is to compare the efficacy of medication for treating pediatric Major Depressive Disorder (MDD) relative to the efficacy of CBT alone, cognitive-behavior therapy (CBT) in combination with medication (COMB) and pill PBO (PBO). The active medication in this study is fluoxetine (Prozac, manufactured by Lilly); the inactive medication is matching pill PBO. All patients in the FLX, PBO and COMB groups receive a pill, either fluoxetine or matching PBO; patients in CBT do not receive pills. Hence, the PTM applies to all subjects receiving pills, while the CBT treatment manual applies to those patients receiving a psychosocial treatment. Both pharmacotherapists and CBT psychotherapists will become familiar with the CBT and PTM manuals so that the treatments may be distinguished with respect to those elements held in common and those that are sharply delineated.

In this context, the PTM presupposes detailed knowledge of the study protocol as defined in the TADS protocol, the CBT Manual, and the Clinician Assessment Manual, including but not limited to the sections directly related to pharmacotherapy of MDD.

1.3 Background of PTM:

Medication will be provided according to conditions set forth in the Pharmacotherapy Treatment Manual (PTM). This PTM was adapted from the Pharmacotherapy of OCD Manual used in the March/Foa Treatment of Pediatric OCD study; (2) the Clinical Management-Medication Administration Manual (CMMAC) used in the Foa/Liebowitz adult OCD study, which in turn was based on the NIMH Treatment of Depression Collaborative Research Program pharmacotherapy treatment protocol; and (3) the Medication Treatment Manual from the Multimodal Treatment of ADHD study (MTA).

1.4 Relationship of MED and CBT in COMB:

CBT and medication management begins simultaneously, with visits time-linked to reduce patient/parent inconvenience and increase compliance. With the exception that medication dose adjustment at a CGI-S = 3 in patients receiving COMB provides for discussion between the pharmacotherapists and psychotherapist regarding the patient's overall trajectory of improvement or lack of same, CBT and medication management will be conducted according to protocols that independently escalate the intensity of treatment over time; i.e. there are no treatment dependencies. Stated differently, with the noted exception, changes in the nature or intensity of CBT or MED management in subjects receiving both treatments (e.g., the COMB group) do not depend on the other treatment. Rather, integration depends solely on

implementing the CBT and pharmacotherapy procedures as specified in the respective treatment manuals.

1.5 Role of Primary Caregiver(s):

Parents are centrally involved at all medication visits. Parents check in with the pharmacotherapists at the beginning of each session, and provide (and are provided) feedback about the patient's progress in treatment. Thus, when we speak of the patient, we are including parents where appropriate. While parents are encouraged to praise the patient for successfully coping with MDD, specific psychotherapeutic interventions by the pharmacotherapist directed at parents are prohibited by the PTM.

2.0 Aims of the PTM

2.1 General Aims:

In order to provide valid data with which to assess the efficacy of the treatments and with which to address other major questions posed by this study, 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 medication treatment condition and to outline the procedures involved in the optimal delivery of medication. The PTM has been designed to resemble as closely as possible the manner in which medications would be most effectively administered in the clinical management of outpatients and adolescents with MDD. Additionally, the interpersonal transactions of the pharmacotherapist and patient have been defined so that the PTM will overlap minimally with insight-oriented or behavioral psychotherapy.

2.2 Specific Aims:

The first goal of the PTM is the effective use of pharmacotherapy to decrease depressive symptoms, alleviate related functional impairment and enhance the quality of life of study patients. The second goal of the PTM 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. Maintaining a low attrition rate is crucial in producing reliable and valid data. Hence, the third major goal of the PTM is to promote the patient's continuation in the study throughout the entire 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.

3.0 Overview of PTM

3.1 General Organization and Focus:

The pharmacotherapist must be responsive to the patient's complaints and needs while also maintaining control of the structure of the treatment. 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 pharmacotherapy session. The appropriate sequencing of clinical inquiry and therapeutic discussion also is 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. In considering the issue of initial focusing, it is important to remember that the patient is 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 patient's Major Depressive Disorder. A therapeutic agenda can thus be established on which to base treatment expectations consistent with principles of high quality medication management.

3.2 Difference from CBT:

The appropriate organization and structuring of the PTM sessions together with the inclusion of the appropriate content should sufficiently distinguish pharmacotherapy from psychotherapy and so help prevent the pharmacotherapist from straying into "psychotherapeutic territory." We do not wish to encourage an interview structure of process so rigidly structured as to preclude opportunities of empathy, support, and those naturally spontaneous and more casual exchanges that permit treatment to be carried out in a warm and truly humane way.

Table One: Pharmacotherapy (PT) Office Sessions*

Timing	Topic	Form
Beginning	Review ADS and CGI score profiles	PTT
	Welcome and check-in	
Middle	Review ADS	ADS
	Assess compliance with medication	MD, MCL
	Review CML and CTL	CML, CTL
	Complete patient safety forms as needed	AEF, SAE, ASAP Log, PSML
	Assign CGI-S and CGI-I scores	CGI-S, CGI-I
	Assign CGAS scores	CGAS
	Medication Rx	MD
End	General encouragement	
	Appointment for next visit	
	Complete Treatment Blindness Form (wk 6 & 12)	PT Blindness
	Complete PT office checklist	PT Office Flow
	Complete Patient Treatment Note	PT Office Note

***Notes**

- If the patient is receiving both CBT and Medication, the preferred treatment order is **PT followed by CBT**.
- Before the session, the pharmacotherapist should review the Pharmacotherapy Therapy Summary Table (PTT), which can also be reviewed with the patient as indicated clinically.
- The adolescent will complete the self-report section of the ADS. Only the PT therapist will provide the symptom severity ratings. After the PT session, the PT will give the completed form to the CBT therapist. Thus, symptom severity information will be available to both therapists.
- The Medication Count Log (MCL), Concomitant Medication Log (CML), Concomitant Treatment Log (CTL) will be completed by the study coordinator prior the patient meeting with the pharmacotherapist.
- Patient safety forms will be completed with the assistance of the SC in the AE/ASAP manual.
- Procedures for completing the ADS, CGI scores and the CGAS are discussed in the Clinician Assessment Manual (CAM).
- Procedures for managing patient safety are presented in the AE/ASAP and Suicide Prevention manuals.
- Although the pharmacotherapist completes the ADS, the CBT therapist will be the primary clinician who will manage ASAP psychosocial interventions for children in COMB.
- The adolescent will complete the Medication Diary (MD) at home and bring it to the session.

3.3 Procedures:

Procedures for structuring each pharmacotherapy session are outlined in Table One. Patients will have one pharmacotherapist throughout the study who, in addition to monitoring clinical status and medication effects, will offer general encouragement regarding the expected benefits from treatment. However, psychotherapy procedures targeting MDD or any other psychiatric or non-psychiatric (e.g. parent –patient) problem are specifically prohibited. Patients will be monitored weekly for medication adjustment based on a standardized escalating dose schedule. Except for the first visit, which will last 50 minutes so that the pharmacotherapist can review the rationale for treatment, all pharmacotherapy visits will last 20-30 minutes. At each visit, the pharmacotherapist will inquire first about general benefits, and then about specific levels of any improvements in affective symptoms (depression and mania) indexed on the Affective Disorders Screen, associated distress and dysfunction, and general functioning. Parents will have completed a Medication Diary that will allow the pharmacotherapist to assess medication compliance. The pharmacotherapist will then inquire about side effects before initiating (visit one) or adjusting (subsequent visits) medication. However, to avoid biasing comparison of physical symptoms, which will be inventoried separately, a specific side effect inventory will not be used. Rather, side effects will be inventoried using procedures outlined in the AE/ASAP Manual:

Specifically, at each medication visit (office or phone) the pharmacotherapist will review the following:

- The previous AEF, PSML logs for unresolved events
- The current CML and CTL

The pharmacotherapist will then ask about medication side effects using the following general question: **“Any health or other problems this week?”** Having explored the nature of these problems, including potential medication side effects, the pharmacotherapist will complete an AEF only for those symptoms reported by the patient that met AE reporting criteria. On the AEF, the pharmacotherapist will then indicate his/her opinion as to whether the reported AE was medication related, the strength of this opinion and whether and what if any changes in medication (e.g. dose, timing) were made.

Consistent with good medical practice, every effort will be made to use the most effective, best tolerated dose of fluoxetine. Dose increases will be delayed or doses reduced for clinically significant side effects, e.g. side effects producing both distress and dysfunction, for which the clinician and the patient/parent believe dosage reduction is indicated. The dosing schedule uses a flexible dose schedule, adjusting the dose upward according to CGI Severity score and down as a function of side effects within a fixed dosing range.

At the conclusion of the visit, the pharmacotherapist must emphasize that medication will likely help the patient feel better during the coming week unless the patient is already normalized in which case the expectation is for continued benefit.

3.4 The Patient’s Role

The patient’s cooperation is essential to the success of the medication treatment program. The groundwork for encouraging compliance must be laid early. The entire research staff must convey to the patient their genuine respect and consideration for him/her as a person. When the patient and his/her parents are together in the same room, questions, explanations and advice should be directed towards the patient as much as possible. Most parents are pleased to see the pharmacotherapist give this kind of consideration to their patient and are content to get most

of their information by “listening in”. They, of course, should also be given a chance to ask any questions on which they may wish additional clarification.

Patients may refuse to participate for a variety of reasons. In some cases, it is the taste of the medication or difficulty swallowing pills. In others, it is a matter of principle: the patient is not willing to admit that there is anything wrong with him/her for which he/she needs medication. Alternatively, the medication becomes a new focus for a long-standing power struggle between parents and patient, akin to conduct/oppositional symptoms. Since the patient’s resistance to taking medication is a common cause of therapeutic failure, the pharmacotherapist must cultivate the patient’s cooperation in order to negotiate a medication contract directly with the patient. This must be done with the knowledge and consent of his/her parents, of course, and in their presence where necessary.

Occasionally, despite the pharmacotherapist’s best efforts to gain the patient’s cooperation, he/she may be unwilling to consider the necessity of taking medication, even though he/she signed the assent form and his/her parents are willing participants in the study. When this happens, it is crucial for the pharmacotherapist to ascertain the reasons for wishing to discontinue medication. Common reasons include lack of benefit, tedium of the research protocol, side effects, or conflict with parents around non-study related and/or study-related issues. It is particularly important to inquire about sexual side effects (without parents present if necessary), as these may comprise the “real reason” for non-compliance. Assuming that there are no reasonable reasons for non-compliance, such as a previously undocumented side effect, the pharmacotherapist should (firmly but not coercively) attempt to persuade the patient to comply, usually emphasizing the value of taking medication for MDD and of taking part in the research study. It is especially important to bypass the possibility of entangling the medication in a long-standing oppositional-defiant interaction between patient and parents. Few kids can turn down an appeal from a pharmacotherapist who has been treating him/her with respect and consideration. Impulsive, sporadic, transient refusals, often confined to a single treatment component or time, do not constitute a considered withdrawal of assent for the whole study. If a patient makes a considered, non-impulsive decision to withdraw assent, this should be honored; however, this is extremely rare after a well-informed initial assent.

4.0 Initial Session

The initial patient visit, which should last approximately 50-60 minutes, will occur immediately after the Gate C2/T0 orientation visit or, for some patients in COMB, who have their first CBT visit then, within two or three days of the orientation visit. During this session the pharmacotherapist will attempt to establish a positive relationship with the patient and parents in the context of a thorough discussion of MDD. The discussion of the past history and current problems will focus on elaborating information about clinical symptoms of Major Depressive Disorder and the related impairments in functioning and decrements in quality of life. Using the ADS as the focus, considerable attention will be devoted to establishing target symptoms as a basis for ongoing clinical assessment and management within the framework of pharmacotherapy.

In all phases of TADS, adjusting medications depends on assessment of depressive symptoms and side effects. Hence, the accurate and comprehensive establishment of target features is necessary if the pharmacotherapist is to understand how well the patient is doing in treatment. Target symptoms will be ascertained by information obtained at baseline assessment (Gate C) and by the ADS, which will be introduced at this visit along with procedures for medication monitoring using the Medication Diary (MD) and pill counts. Since considerable information has already been gathered during eligibility assessment, the review of this assessment information from eligibility determination prior to the first visit will speed this process considerably. In

addition to providing material for future sessions, discussion of target features will help structure sessions so that active psychotherapeutic interventions can be avoided, thus keeping the pharmacotherapy sessions as free from “psychotherapeutic contamination” as possible.

A comprehensive determination of target and accessory features will also be necessary for later detection of study medication side effects, which may affect the titration schedule by limiting dose increases as noted below. Review of procedures for managing side effects will serve as a vehicle for discussing concerns that patients and parents have regarding medication-related adverse events.

A basic and easily understandable explanatory model of how and why fluoxetine may be 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 Major Depressive Disorder should be explained. Specifically, fluoxetine, like other serotonin reuptake inhibitors, has a high likelihood of reducing depressive symptoms across mood, thinking and neurovegetative symptoms. These medications may work by altering central nervous system serotonin activity and sensitivity, since the serotonergic drugs seem most helpful for Major Depressive Disorder as shown in controlled clinical trials. It is important to emphasize the scientific underpinnings of the trial or, stated differently, the proven benefit of medication management.

Resistance to the idea of medication should be asked about, and if present, 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 ambiance 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 questions from the patient/parent with further clarification and support.

If present, it is critically important to review the 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 psychotropic agents, 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 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 might be 8 to 10 weeks before a therapeutic response emerges. The concept of progressive improvement should be discussed so patients do not unrealistically expect an early “all or none” response.

The possibility of and mechanism for managing side effects during treatment should be discussed. **Pharmacotherapists should mention the side effects that most frequently occur during treatment (nausea, diarrhea, insomnia, fatigue, headache, tremor, rash). 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 and the patient evaluated. 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.

Note that the patient and parent should be informed that a study clinician will be “on call” for the study at all times.

It should be emphasized that the treatment is based on specific therapeutic effects and that the medication is not a nonspecific sedative or tranquilizer. It should also be made clear that the medication is not addictive and that, although the rationale for its use may not be understood by many lay people, its use is grounded in scientific evidence that mood disorders 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 substantial percentage of patients but that the treatment will be reevaluated should any sustained worsening of symptoms occur. The patient should be advised that other medications (e.g., tranquilizers and sedatives, alcoholic beverages, other drugs of abuse, such as marijuana, proprietary medications, hormone supplements, excessive caffeine, and mood altering medications, such as St. John’s Wort, etc.) should not be ingested during the course of treatment. It is especially important to point out that fluoxetine may interfere with the metabolism of other drugs, which means in practice that parents/patients must point out to other doctors, who may be seeing the patient for a medical problem, that the patient is taking fluoxetine so that potential adverse drug:drug interactions may be avoided.

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 disorder features, and possible side effects, as well as to discussing 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 scheduled 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 and to come in for an unscheduled visit if necessary.

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 features with the idea of positive therapeutic outcome as a result of pharmacotherapy. By assisting the patient in developing a positive set of hopeful expectations linking the relief of core features with medication effects, the pharmacotherapist creates opportunities for ongoing therapeutic discussions focused on those aspects of the medical treatment of Major Depressive Disorder that are personally important to the patient.

4.1 Example:

Here we would like to present a brief sketch of an ideal first session. In such an idealized version of the initial 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 pharmacotherapist should also demonstrate knowledge about the study in general.

When the patient has been assigned to combination treatment, the pharmacotherapist should acknowledge the possible synergistic benefits of combining fluoxetine and CBT, while emphasizing that the two treatments are conducted independently. Also, in the COMB

condition, the pharmacotherapist should (1) explicitly note that the medication being given will be fluoxetine (and not pill PBO) as some patients may still wonder whether drug is active or inactive, and (2) that he or she will be talking to the patient's psychotherapist about how things are going for the patient during the study so that the dose of medication can be adjusted appropriately.

After reviewing the patient's diagnostic summary and going over the ADS symptom checklist with the patient and parent, the pharmacotherapist should establish clinically a set of care or target symptoms, manifestations of the underlying disease process which will serve as indicators of potential response to the treatment that will be prescribed. MDD related impairments in functioning and limitations of quality of life can be simultaneously elicited. Screening for the medication side effects awaits the second visit; however, instruction about how medication side effects will be managed should be used to inform the patient/parents about what side effects to watch for and about how medication will be monitored during the study.

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, family or cognitive-behavioral incursions and digressions that not only violate study protocol but may also be "anti therapeutic," 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 20 minutes are available for the pharmacotherapist to establish and convey a sense of authoritative responsibility and knowledge about pharmacotherapy, to appropriately educate the patient about how and why the medication can help, and to allow for questions from the patient/parent(s) and further discussion.

5.0 Second and Subsequent Sessions

At the second and subsequent sessions, the pharmacotherapist will meet with the patient for 20-30 minutes following procedures outlined in Table One above. Using the ADS, a systematic inquiry in the presence and intensity of the already established target features that characterize the patient's Major Depressive Disorder and its related disability should provide the basis of 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.

Using clinical inquiry as a guide, the pharmacotherapist will inventory and rate all side effects present that week, coding each adverse event meeting AE criteria as likely drug induced or not on the AEF and PSML. 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 likely 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 side effects, especially in patients who are sensitive to the study medications and/or apprehensive about taking medication. Further educative efforts regarding the "hows" and "whys" of medication may be helpful and perhaps necessary to avoid dropouts and/or noncompliance during the early stages of the pharmacotherapeutic treatment.

5.1 Titration of Study Medication

Assessment

Patients will have one pharmacotherapist throughout the study who, in addition to monitoring clinical status and medication effects, will offer general encouragement about the effectiveness of pharmacotherapy for MDD. Except for the first visit, which will last 50-60 minutes so that the psychiatrist can review the rationale for treatment, all pharmacotherapy visits will last 20-30 minutes. Parents will complete a Medication Diary (MD) and pill counts, and the pharmacotherapist and/or study coordinator will conduct pill counts at treatment visits, which will be used to assess drug compliance.

Except in emergencies, patients and clinicians remain blind to medication status during Stage I of the study. At each visit, the psychiatrist will inquire about benefits and side effects before initiating (visit 1) or adjusting (later visits) medication. Side effects, including mania, as well as MDD symptoms will be inventoried using a standard clinical interrogatory: "Anything health problems this week?"

With sufficient clinical information about benefits and side effects in hand, the pharmacotherapist will assign a CGI-Severity (CGI-S) score anchored as follows: 1=normal, not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill. The response metric is as follows: full responder is a scale score of 1 or 2; partial/minimal response a 3; and non-response as 4 or worse. Patients entering TADS are expected to have a CGI-S of 4 or greater. The CGI-S will allow the pharmacotherapist to track clinician-rated outcomes on a more frequent basis than the IE ratings.

There will be a PT Table (PTT) placed in the front of the PT chart. Updated by the SC, the PT Table will provide a running summary of the ADS, CGI-I, CGI-S and CGAS scores from previous visits.

Specific instructions for administering and scoring the ADS the CGI-I and CGI-S as well as the CGAS can be found in the Clinician Assessment Manual, with which the pharmacotherapist should be familiar.

Although convenience may dictate that major and minor assessment and treatment visits occur on the same day, the assessment schedule is independent of the treatment schedule. For example, the week 12 assessment visit occurs some time during week 12 irrespective of whether the patient has completed all of the scheduled Stage I treatment visits.

If the assessment and treatment visits are scheduled back-to-back, the IE visit (and preferably all other assessments too) should come before the treatment visit in order not to bias the subject's responses because of proximate (recency) effects from the treatment session.

Treatment Initiation Schedule, Week and Visit Numbers

For all intents and purposes, the Orientation Visit is considered as the "start of treatment" (i.e., the Stage I "clock" begins at this point, which is labeled T₀).

The first week of treatment is labeled week 1, which begins at T₀; visits are scheduled by week of treatment. Visit 1 takes place during week 1 and denotes the start of one week of treatment, whether it be with pills only, CBT or combination. Stated differently, irrespective of the actual number of sessions attended, all patients will be considered to have had an amount of

treatment in weeks equal to the number of weeks completed since T0. Hence, at the week 12 visit the patient would be considered to have completed 12 weeks of treatment, with determination by the clinician regarding whether or not he/she moves into Stage II as a partial or full responder.

To guarantee that patients receive a full twelve weeks of treatment in Stage I, the following **treatment initiation schedule** should be followed if at all possible.

- For patients in pills only conditions (FLX and PBO), the first pharmacotherapy visit should immediately follow the C2 Orientation Visit.
- For patients in the CBT only condition, the first CBT visit should immediately follow the C2 Orientation Visit.
- For patients assigned to Combination treatment, the first pharmacotherapy and the first CBT visit are best scheduled back-to-back immediately following the Orientation Visit. Alternatively, depending on feasibility considerations, the first CBT visit should immediately follow the C2 Orientation Visit, with the first pharmacotherapy visit to follow within two or three days when the patient returns for the second (week 1, visit 2) CBT visit. This schedule is preferable because CBT visits being longer are more difficult to schedule than pharmacotherapy.

Although convenience may dictate that assessment and treatment visits occur on the same day, the assessment schedule is independent of the treatment schedule. For example, the week 12 assessment visit occurs some time during week 12 irrespective of whether the patient has completed all of the scheduled Stage I treatment visits.

Titration and Visit Schedule in Stage I

In the Emslie study, patients received 20 mg, with no option for higher doses; 40% of patients were non-responders. In adult fixed dose studies, no obvious between group benefit from doses over 20 mg emerged, while side effects are clearly greater at the higher doses. In both child and adult studies, subgroups of patients responsive to higher than initial doses have been identified, suggesting that maximizing response rate requires sufficient time to implement high dose strategies.

To best reconcile dose-response and time-action effects, TADS uses a flexible dosing schedule (Table 2) that is dependent on pharmacotherapist-assigned CGI-S score and the ascertainment of clinically significant side effects. **Note this CGI score is assigned for MDD symptoms only.** Relative to normal functioning for an age, race, gender and community matched peers, the CGI-Severity (CGI-S) score will be anchored as follows: 1=normal, not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill. Response requires CGI-S of 1 or 2; partial response a 3; and non-response a 4 or worse.

Fluoxetine is initiated at a dose of 10mg/day and moved to 20mg at week two assuming no limiting side effects. As shown in Table 2, the dose of FLX should be increased at weeks 4, 6, 9 and 12 according to the following CGI-S schedule.

- If the CGI-S score = 1 or 2, no change in dose.
- If the CGI-S score = 3 at week 4 or later, the clinician has the option to leave the dose the same or increase it to the next higher dose to account for time-response considerations, e.g. to allow for the expected time or trajectory to onset of benefits or resolution of side effects.
- At week 4, the pharmacotherapist has the option to leave the dose at 20mg if the patient has a CGI-S score of 4 **and** has improved from a CGI-S of 6 (severely ill) or 7 (extremely ill) at baseline.
- Otherwise, if the CGI-S score is ≥ 4 , the pharmacotherapist (absent limiting side effects) must increase to the next higher dose in a 10 or 20 mg increment, depending on the week of treatment and on the presence of dose-limiting side effects.
- In partial responders (CGI-S of 3), the dose may be increased by 10 or 20 mg, depending on the starting dose and side effects, to a maximum of 60mg at the week 12 visit.

Table 2: Stage I Dosing/Visit Schedule

Week	Visit Type*	FLX Dose**
T0	Orientation	None
1	Office	10 mg
2	Office	20 mg
3	Phone	20 mg
4	Office	20-30 mg
5	Phone	20-30 mg
6	Office	20-40 mg
7	Phone	20-40 mg
8	Phone	20-40 mg
9	Office	20-40 mg
10	Phone	20-40 mg
11	Phone	20-40 mg
12	Office	20-40 mg

*All but the first phone visit is optional if patient is at CGI-S 1 or 2. Any phone visit may be converted to an office visit if the patient's clinical situation requires it.

**Dose increases may be deferred or doses may be adjusted downward for side effects only.

Dose increases may be delayed or doses reduced for clinically significant side effects, e.g., side effects producing both distress and dysfunction, for which the clinician and the patient/parent believe dosage stabilization or reduction is indicated. All adverse events (e.g. moderate side effects or above) recorded on the AEF/PSML that are thought likely to be side effects should prompt careful consideration regarding delaying a dose increase or decreasing the dose of study drug.

Except for the week 3 phone visit, which is mandated, all phone visits are optional for patients at CGI-S scores of 1 or 2 at the previous office visit. Conversely, phone visits may be converted to clinic visits when the clinician concludes that patient monitoring requires it. Dose increases that were previously delayed because of side effects may be agreed to by phone; all other dose increases require a clinic visit.

Integration with CBT for Patients in Combination Treatment

With the exception of pills-only condition in Stage I, treatment providers are not blind to treatment status. In fact, **sites are expected to review the clinical status of each teenager in TADS in rotation at weekly TADS team meetings.** This offers the opportunity to integrate aspects of CBT and medication treatment for those children assigned to COMB. For example, patients at week 6 who are partial responders could escalate in dose or stay the same, with the decision in part turning on how well the CBT therapist believes the patient is progressing in CBT.

To allow limited integration between medication management and CBT, we will use the following decision rules:

- CBT is functionally independent of medication management, e.g. no decisions regarding the CBT protocol depend on decisions regarding medication management.
- For all dose increases other than those depending on a CGI-S of 3, the protocols for administering medication and CBT are functionally independent.
- When the CGI-S = 3, e.g. partial response, the pharmacotherapist should consult with the CBT therapist at the weekly TADS team meeting, where it is expected that all TADS patients will be discussed in rotation, or at another time of mutual convenience. This discussion, the goal of which is consensus between the pharmacotherapist and CBT therapist regarding FLX dosing, should center on the following: (1) whether the patient is making good use of CBT and, in that context, (2) whether the change trajectory for MDD symptoms over time suggests that a dose escalation is warranted or whether it would be prudent, especially if side effects are bothersome, to delay a dose increase until it is clearer that the patient is not progressing as expected for a hoped for treatment responder. In the unlikely event of disagreement, the pharmacotherapist will decide the dosing strategy to be followed.

Dosing and Visit Schedules in Stage II

As discussed in the TADS protocol, patients with a clinician assigned CGI-S score \geq exit TADS treatments at the end of Stage I.

As shown in Table 3, patients with a CGI-S score of 1 or 2 at the end of Stage I will continue on the same dose of FLX at a reduced visit schedule during Stage II.

By contrast, if at the end of Stage I the CGI-S score is 3, indicating partial response, then the Stage II dose may be increased at visit 13 (if not already increased at week 12) by a minimum of 10mg and a maximum of 20mg over the Stage I ending dose, with a maximum Stage II dose of 60mg. For example, if a subject ended Stage I as a partial responder at 40mg, the pharmacotherapist could increase the dose to 60mg, assuming no side effects. If minor side effects were present, the pharmacotherapist might

Table 3: Stage II Dosing/Visit Schedule

Week	Responders*	Partial Responders	FLX Dose**
13	--	Office	20-60mg
14	--	Office	20-60 mg
15	Office	Phone	20-60 mg
16	--	Office	20-60 mg
17	--	Phone	20-60mg
18	Office	Office	20-60mg

*Phone visits are optional for responders; mandatory for partial responders following a dose change.

**For partial responders, a dose adjustment upward by a minimum of 10 and a maximum of 20 mg every other week is permissible; otherwise, dose may be adjusted downward for side effects only.

elect to increase the dose to 50mg rather than 60mg or to leave the dose at 40mg, depending on patient and doctor preference.

Dosing and Visit Schedules in Stage III

Stage III medication patients will be followed every six weeks with 20-30 minute medication visits. Other than downward adjustment of the dose for major or prohibitive side effects, no adjustments to the dosing regimen arrived at in Stage II are permitted. If a patient worsens in Stage III with either an associated clinical crisis or threatened attrition, a dose increase in FLX up to 60mg maximum dose may be undertaken using ASAP procedures.

Dosing and Visit Schedules in Stage IV

With its long half-life, withdrawal symptoms are not problematic with FLX. Hence, medication can be discontinued abruptly in FLX treated patients at the end of Stage III if discontinuation is in fact recommended.

Discontinuing FLX

Since fluoxetine is unlikely to produce an SSRI withdrawal syndrome—nausea, diarrhea, sleep disturbance, somatic/autonomic symptoms and cognitive/affective—it is not necessary to taper medication, e.g. the medication can be stopped abruptly. However, should withdrawal symptoms develop, study drug may be discontinued over 2 weeks by decreasing by $\frac{1}{2}$ the dose at 1 week intervals. For example, a patient on 40mg of study drug would drop to 20mg for 1 week, then no drug after one additional week. Under no circumstances should the taper be slowed or stopped because of patient/parent anxiety about relapse unless, of course, the patient has in fact relapsed in which case the procedures for managing relapse should be implemented. Patients discontinuing FLX should be cautioned not to begin an MAOI or to start St. John's wart within 6 weeks of stopping drug. Patients should also be cautioned regarding the potential for drug:drug interactions (through the 2D6 and 3A4 mechanisms, in particular) and to tell their treating physician about this for at least six weeks after discontinuing FLX.

5.2 Drug Packaging

During Stage I, fluoxetine and matching PBO in 10 mg doses will be packaged in bottles containing sufficient medication at a maximum of 40 mg per day for 1 week (10mg x 4 pills x 7 days = 28 ten mg tablets). During Stages II and III, fluoxetine will be packaged in 40 or 60mg dose increments, depending on clinical status. Study medication will be prescribed each week to be taken at the same time each day. One week of study medication at maximum Stage II dosing (10mg x 6 pills x 7 days = 42 ten mg tablets) will be provided to cover the possibility of a missed appointment by the patient or pharmacotherapist. Patients are instructed to return all unused study medication to the therapist or study pharmacotherapy monitor at each session. Using the Medication Diary (MD) and the Medication Count Log (MCL), the physician and pharmacotherapy study monitor must maintain an accurate record of all unused study medication. The amount of medication prescribed and the amount of unused medication will be recorded at each session using this form, which also allows the pharmacotherapist to schedule medication for the ensuing week(s).

6.0 Pharmacotherapy Management Issues

6.1 Other medications:

Patients stabilized and managed on a psychostimulant (methylphenidate or dexedrine) may be admitted into the study if their medication regimen is appropriate with respect to dose-response and time-response parameters and has not been changed for two months prior to

randomization. Specifically, the TADS protocol requires the following conditions to be established prior to randomization:

“Stable treatment with a psychostimulant (Adderall or IR or sustained methylphenidate or Dexedrine; pemoline and methamphetamine are excluded) for ADHD is acceptable under the following conditions. First, stable means that total daily dose has not changed by more than 25% during the 12 months preceding study Gate B consent. Second, written agreement is obtained from the patient’s prescribing physician between Gates B and C to collaborate with TADS procedures for managing psychostimulants during TADS. For subjects in pills conditions, this means ceding control of stimulant treatment to the study pharmacotherapist. In the CBT alone condition, the prescribing physician continues to monitor psychostimulant treatment within three parameters: (1) change in psychostimulant type of greater than 25% total daily dose is not permissible without prior consultation with the CBT therapist; (2) treatment with other psychotropic medications or recommendations regarding the need for additional or changes in psychotropic medication is not permissible; and (3), additional psychosocial treatment or recommendations regarding changes in psychosocial treatments is permissible. Note: If additional treatment for ADHD outside the TADS protocol becomes necessary on an urgent or emergent basis, such treatment will be provided as required under ASAP provisions and, if needed, by referral to community care. (Gates A and B)”

Responsibility for management of psychostimulant medication will fall to the TADS pharmacotherapists, but the cost of the medication will be borne by the patient.

In general, the TADS pharmacotherapist will follow the same guidelines as enumerated for an outside pharmacotherapist: : (1) change in psychostimulant type of greater than 25% total daily dose is not permissible without prior consultation with pharmacotherapy supervisor; (2) treatment with other psychotropic medications is not permissible; and (3), additional psychosocial treatment or recommendations regarding changes in psychosocial treatments is permissible.

All other psychotropic medications administered as treatment for a specific DSM-IV disorder are disallowed during TADS Stages I, II and III. At times, medications administered for a non-psychiatric indication may have psychotropic properties that might conflict with the aims of this Study. Appendix A lists these medications, some of which are permissible on an acute but not chronic basis.

Specific sedative hypnotics that can be used during TADS (but not paid for by the study) are defined in Appendix A.

6.2 Avoiding Adverse Drug Interactions:

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 headaches or laxatives for constipation is acceptable, but the use of prescription medication is not allowed without prior discussion. 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.

As noted earlier, some medications are disallowed either as a prior exclusion at Gate B or during TADS treatment. When questions regarding the appropriateness of a non-psychiatric medication arise during treatment, these should be brought up on the biweekly Cross-Site Pharmacology Panel call. In more pressing situations, the pharmacotherapist and site PI may wish to consult with Dr. March at the CC.

In some instances, adverse drug-drug interactions may occur when FLX is combined with other medications used for medical purposes and which are not contraindicated by the TADS protocol. If such a drug-drug interaction is possible, the pharmacotherapist is mandated to discuss this issue with the prescribing physician.

6.3 Laboratory work:

Other than the pregnancy test during eligibility assessment, no routine laboratory tests are scheduled. At any time during the course of treatment, however, the PTM pharmacotherapist may request laboratory tests (e.g., liver function tests) or may request an evaluation of the patient by a medical evaluator.

6.4 Principles of side effects management:

Overview

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 temporarily lowering the dose. Advice may be given regarding physiological management of side effects (e.g., acetaminophen for headaches). Managing more severe side effects may require a permanent lowering of the dosage. Adjunctive medication for the management of side effects (e.g., yohimbine for orgasmic dysfunction) is not permitted.

Procedures for Inquiring About Side Effects

Procedures for managing adverse events are extensively summarized in the AE/ASAP manual with which the pharmacotherapist is expected to be familiar.

At each medication visit (office or phone) the pharmacotherapist will review the following:

- The previous AEF, PSML logs for unresolved events
- The current CML and CTL

The pharmacotherapist will then ask about medication side effects using the following general question: **“Any health or other problems this week?”** Having explored the nature of these problems, including potential medication side effects, the pharmacotherapist will complete an AEF only for those symptoms reported by the patient that met AE reporting criteria. On the AEF, the pharmacotherapist will then indicate his/her opinion as to whether the reported AE was medication related, the strength of this opinion and whether and what if any changes in medication (e.g. dose, timing) were made.

The pharmacotherapist is expected to coordinate completing the AEF/PSML with the study coordinator per procedures outlined in the ASAP/AE Manual.

Procedures for Dose Adjustment in Response to Side Effects

Specific procedures for managing side effects are presented below. The general principles are as follows:

- For mild side effects, the pharmacotherapist may leave medication administration unchanged or may adjust the timing of medication without changing the dose.
- For moderate side effects, the pharmacotherapist may reduce or alter the timing of any medication dose until side effects are mild or negligible.
- For severe side effects, the medication must be discontinued and appropriate remedies invoked

Side effects are defined as follows:

- Mild side effects are defined as those that emerge spontaneously or on inquiry, are not associated with impairment and so do not need to be recorded on the AEF/PSML and that do not in the opinion of the pharmacotherapist warrant a reduction in dose. An example of a mild side effect might be mild sleep disturbance or mild nausea with change in dietary intake at the beginning of treatment.
- Moderate side effects are similar to mild side effects, but the frequency, intensity or duration is sufficiently great to warrant a reduction in dose but not to prompt discontinuation. Moderate side effects generally interfere with functioning and require recording on the AEF/PSML. An example of a moderate side effect would be persistent nausea, persistent sleep disruption or noticeable akathisia that interfere with school functioning.
- Emergence of a severe side effect automatically requires discontinuation of medication and, if needed, provision of treatment to manage the offending side effect. Examples of severe/prohibitive side effects include mania, severe nausea and vomiting with weight loss not manageable by dose reduction or severe sexual side effects not manageable by dose reduction.

To insure cross-site consistency in the administration of medication, the overall profile and site specific profile of medication changes in response to side effects will be reviewed periodically on the CSPP call.

The PTM dosage schedule is designed to optimize the possibility of a full response to the study medication by specifying a semi-flexible upward titration to maximum doses of fluoxetine, taking into consideration limiting side effects. Because side effects may be more likely with forced upward titration schedules, the dose escalation strategy in Tables Two and Three give patients time to acclimate to each dose level before further increase. At the same time, dose escalation cannot be too slow or patients will grow discouraged before reaching potentially therapeutic levels. In addition, a substantial time period on maximum dose of any medication is desirable during the acute treatment stage to permit meaningful assessment of response to that drug. At any dosage, if the patient manifests severe side effects that appear dose related, this may signify that a lower dose is the maximum tolerated dose at that time. If side effects are greater than mild and the patient/parent is in agreement, the dosage should be increased per the dosage schedule for that drug. The time of day at which a drug is given may be altered to minimize side effects. With the exception of dose reductions because of side effects, the end of Stage II dose becomes the Stage III maintenance dose. The potential range of dosage

combined with flexibility in the dosage schedule should assure an adequate trial of medication for each patient.

Switching to Mania

An uncommon but specific side effect of medication treatment for depression is switching from depression to mania. In contrast to depression, which is characterized by sad or low mood and no energy, mania is characterized by elevated rather than depressed mood and can be accompanied by more energy, less need for sleep and troublesome activities, such as increased sexual activity or drug use. Return to normal mood is not mania, even if the patient appears irresponsible, since normal mood may "take some getting used to." Similarly, elevated mood in hypomania can be distinguished from mania by the fact that hypomania does not interfere (and sometimes augments) functioning.

Using the ADS, the pharmacotherapists will monitor patients carefully throughout the study for the emergence of manic symptoms. For the purpose of TADS, a diagnosis of mania will be made using DSM-IV criteria guided by the K-SADS criteria to make the diagnosis. If mania occurs, patients must be withdrawn from the study and be offered additional interventions outside the study.

Between Visit Management of Side Effects

If troublesome side effects emerge as the dose is being increased, the patient should be instructed to contact the pharmacotherapist. Several alternatives are then available. For example, 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.

When changing dose because of side effects the following steps are advisable:

Step One: The criterion initiating an alteration in medication regimen begins with an event or events that lead the pharmacotherapist, subject or parent to note the possibility of excessive side effects. This first sign will be said to occur when the pharmacotherapist learns of the "event," which might, for example, include a new side effect or increase in a previously tolerated (mild) side effect. Note that an event prompting a medication change may occur in the context of an unscheduled contact with the family or in a scheduled continuing treatment clinic visit.

Step Two: The pharmacotherapist will respond to this alert by calling the patient/parent back the same day or next day to obtain more details of the "event or events." The pharmacotherapist will check to determine if there are immediate causes of this event, including lapses in medication compliance or intercurrent medical illness, for example, headache or vomiting associated with a viral gastroenteritis.

Step Three: Absent moderate or severe side effects, which require prompt changes in medication and AE recording, the pharmacotherapist may advise the parent or patient that mild temporary side effects are not uncommon, and simply bear watching. Severe side effects require drug discontinuation and, consequently, an office visit the same day. Given a moderate side effect, the pharmacotherapist may chose to adjust the medication dose or timing by phone, calling the patient back in a day or two to check on the results of the dose manipulation, or to see the patient to further determine the appropriate course of action. Otherwise, the pharmacotherapist should arrange to see or to talk to the patient in 5-7 days at which time, if the side effect persists, the dose should be adjusted and the side effect recorded in the AEF and PSML.

Since the primary goal of PTM is good clinical management of the patient, patients who cannot tolerate fluoxetine because of side effects that are dose-dependent, and who have not improved or have deteriorated despite a reasonable but slow escalating dose titration trial, may need to be withdrawn from the study at the discretion of the parent/pharmacotherapist.

6.5 Avoiding Dropouts:

The avoidance of premature termination and/or dropouts from the medication alone conditions (fluoxetine and pill PBO) 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 6 weeks.

6.6 Between Visit and Emergency Phone calls:

Especially during the early weeks of treatment, the pharmacotherapist or associate must be available to the patient for telephone calls between appointments for questions about side effects that may occur as medication dosage is increased. Hence, phone calls to the patient or parent from a study clinician are scheduled as outlined in Tables 2 and 3, with follow-up by the pharmacotherapist in the office as needed. 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 pharmacotherapist is managing the patient's medication regimen. 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 feelings of 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.

As defined by the visit schedule in Tables 2 and 3, pre-arranged phone calls will be made by the pharmacotherapist to the patient and/or parent, but preferably the patient, during Stages I and II of the study. The purpose of these calls is to "check in" regarding clinical status and to make a determination regarding whether a change in dose or timing of administration is required. **To avoid unduly burdening patients or doctors with unnecessary activities, all but the first of these calls are optional for patients doing well in treatment (CGI-S = 1 or 2).** If the patient is stable or improving, the pharmacotherapist should support the improvement as being associated with taking medication and remind the patient of the next scheduled visit. If the patient is worse, the pharmacotherapist should make a determination of whether an office visit is required for further evaluation. These scheduled/optional phone calls do not count against the bank of ASAP calls. **Note that phone visits should not be substituted for office visits for convenience only.**

A change in medication by phone may be undertaken if one of the following conditions is present: (1) a dose reduction is needed because of side effects; (2) a dose increase that previously was deferred because of clinical status (CGI-S \geq 3) is now warranted on the basis of clinical condition (CGI-S = 3, e.g. mildly ill); or (3) a dose increase that was deferred because of side effects is still indicated because of clinical status (CGI-S = 3, e.g. mildly ill). These dose changes will be tracked on the Medication Count Log (MCL) at the next office visit.

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 pharmacotherapist 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 the back-up pharmacotherapist at that site. Phone calls are not to constitute supplementary or adjunctive therapy.

Using the standard form for recording medication visits, the pharmacotherapist should keep an accurate record of every phone call made to or 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).

6.7 Clinical Deterioration:

Despite our best efforts, some patients will continue to exhibit grossly impairing psychiatric symptomatology so that a parent/patient believe that medication will not likely be of sufficient benefit and that continuing medication management is not warranted. In this instance, or when the clinician in consultation with the site PI believes that a patient should be withdrawn from the study, ASAP procedures (see the TADS protocol and the AE/ASAP manual) should be invoked. In consultation with the site PI, 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.

More commonly, patients and/or parents may experience transient exacerbation of symptoms or persistent difficulties that do not threaten study participation but that nonetheless call for additional interventions by the pharmacotherapist. An example might be the patient who is up all night and has difficulty getting to school for whom moving FLX to the morning has not sufficed, making simple instructions regarding sleep hygiene or perhaps an approved sedative-hypnotic necessary for the patient. Another example might be the patient who has role disputes or sibling conflicts that are sufficiently distressing to the parent to warrant standardized instructions to the parent beyond reassurance that it is important to wait for the medication to "kick in." For these and other similar problems in MDD target symptoms, the pharmacotherapist should provide **common-sense advice** within the framework of the PT visit. Such advice should be similar to what would be available from any competent pharmacotherapist regarding managing problems typical of those seen in teenagers with MDD without straying into CBT, IPT, dynamic psychotherapy, family therapy or any other form of structured psychosocial intervention. For example, brief suggestions regarding a regular bedtime, quiet room, comfortable temperature and avoiding caffeine or arousing activities before bed are appropriate whereas relaxation training or setting up a structured bedtime routine are not. For subjects in the Combination treatment arm, adjusted CBT interventions often will supplant interventions by the pharmacotherapists, which in any event should be coordinated by discussion at the weekly TADS team meeting.

When this is not sufficient and the possibility of early termination or patient-initiated protocol violations, such as seeking outside treatment, supportive treatment as defined in the ASAP manual is permissible for subjects meeting ASAP referral criteria. The pharmacotherapists can administer supportive ASAP interventions, e.g. crisis management. For more complex interventions, such as CBT for panic disorder, the ASAP panel will make a referral to a suitable treatment setting not associated with the study. Although the ASAP Panel must approve referral, the study clinician most closely associated with the child will make the actual referral. The referral can be to another clinician at the site's clinic, but not to anyone on the study staff.

As defined in the ASAP procedures, there will be an extra full assessment (endpoint) for premature termination just prior to receiving non-protocol treatment. This special assessment

will include all assessments scheduled to occur at the next full assessment point. If it occurs within a month of the next regularly scheduled assessment, it will replace that regular assessment.

Pharmacotherapy as defined in the PTM may or may not continue in the face of ASAP procedures.

Irrespective of whether the patient continues to be followed within the medication arm for treatment purposes, all such subjects will continue to receive regular assessments. The pharmacotherapists should remind the patient and parent that they agreed to this in advance of randomization and that the additional assessments will be free, will be important to the research goals of the study and will potentially be of benefit to the patient.

6.8 Research/Study Termination

Even though active psychotherapy as such is not provided in the PTM, a significant doctor-patient relationship will likely develop during the study. 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. If, at any time during the course of treatment, the patient inquires about continuing treatment beyond the study period, he/she should be reassured that an appropriate follow-up will be provided depending on the outcome and what treatment he/she has been on. Similarly, questions by the patient the purpose and design of the study should be answered in a matter-of-fact fashion consistent with the information supplied during informed consent.

6.9 If the Patient is a Non-responder

At the week 12 visit, a clinical determination will be made about whether the patient is a responder, partial responder or non-responder to study treatment. Procedures for managing referral at the end of Stages I or III or on premature termination are presented in the TADS protocol. **To avoid biasing the week 12 assessment visit, the IE visit and preferably other assessments as well should come before this visit for all patients, but especially those patients for who TADS treatment will stop. This would include pills only patients who may be on PBO.**

Stage I

If the patient is a non-responder (CGI-I of 4 or worse) at the end of stage I and/or was assigned to pills only, the study blind is broken so that the Pharmacotherapist can determine if the patient is a non-responder to fluoxetine or had been randomized to the PBO group. If the latter and the patient is a non-responder, the patient should be offered 12 weeks of open-label treatment with fluoxetine, open CBT or their combination, whatever the patient/family prefer, from the study team. If patient is a responder, the patient should be referred to open community treatment as outlined in the protocol and brought back only for full assessments as outlined in the TADS consent procedure.

Stage III

Patients at the end of Stage III will be given recommendations for further treatment depending on clinical status. At the end of the study, patients will be classified by the study team into recovered (Level 1), partial responder (Level 2) or non-responder (Level 3). Based on treatment assignment, the site team will make recommendations regarding appropriate care for the ensuing year of open follow-up.

6.10 If the Patient is a Responder at the End of Stage I or II

At the week 12 Stage I visit, the determination may be made by the clinician that the patient is a responder (CGI-I= 1 or 2) or partial responder (CGI-I= 3) to study treatment, either medication alone (fluoxetine or PBO) or combination treatment. Except for PBO responders, who advance to open follow-up per the protocol, the patient will advance to Stage II at his or her current dose. Partial responders (CGI-I= 3) advance to Stage II at a higher dose of fluoxetine per the dose escalation protocol outlined in Tables 2 and 3.

Since it is possible for a responder to medication alone to be receiving either fluoxetine or PBO, the blind will continue through Stage I. In Stage II, all drug treatment is open.

6.11 The Cross-Site Pharmacology Panel (CSPP)

The CSPP teleconference will observe the following procedures:

Goals: The goals of the CSPP are to: (1) insure high quality clinical care, and (2) decrease the potential for cross-site variability, by closely monitoring treatment fidelity for medication administration to subjects in the medication arms of the study.

Changes in timing or dose of medication: To insure that treatment is administered identically at all sites, the number and status of all children undergoing medication changes will be monitored in real time using the Medication Count Log. Specifically, inclusive of protocol-driven increases in medication, all changes in the timing or dose of medication will be reviewed monthly on a post hoc basis by the CSPP. The CSPP will use the Adverse Event Log (AEF) as the organizing rubric for discussing medication changes that emerge in response to concerns about side effects. To reduce cross-site variability within the medication-only treatment arm each site will present one case, chosen to illustrate a particular clinical dilemma of the site's for discussion by the CSPP. The extent to which a pharmacotherapist initiates dose changes will be monitored by the CC. Based on review of this data, sites with dose change frequencies that are higher or lower than expected will be queried by the CC and reasons for the discrepancy will be explored on the CC call.

Frequency and time: The CSPP will meet on a monthly basis by teleconference, one Thursday of each month immediately before the regular Thursday PI call. Initially, The CSPP teleconference will be scheduled for 30 minutes, with adjustments in length depending on need.

Membership: The CSPP will consist of the site pharmacotherapist and pharmacotherapy supervisor plus Dr. March from the CC. Members will be selected by the site, and can be re-nominated. To insure full site participation, each site also will nominate an alternate member to the CSPP, who will participate if the primary member is unavailable. Eligibility for CSPP membership will be met by the following professional background: child psychiatrist, pediatrician, nurse practitioner, or physician's assistant, all of whom must be state licensed to prescribe medications. In the case of physician extenders, supervision for CSPP participation must correspond to the licensing requirements set by the state in which the site is located.

Chair: Dr. March will Chair the CSPP. Each year members will select (one vote per site) a vice-chair from among the site representatives who will chair monthly CSPP teleconferences in the absence of the chairperson. Short presentations will be the rule during CSPP teleconferences. The CSPP chairperson will curtail unnecessary discussion.

Minutes: Dr. March will be responsible for the CSPP minutes. In the event, Dr. March is not on the CSPP call, the CSPP vice-chair will prepare the minutes.

Procedures: The CSPP will consider agenda items in the following order: (1) emergencies threatening study participation or posing risk to study participants; (2) brief numerical summary of the number of children on medication in each of the three TADS Stages; (3) post hoc

numerical summary of changes in timing of medication administration or FLX dose; and (4) discussion of specific issues of cross-site variability as indicated by post hoc review of side effects or dosing changes, respectively. If no emergencies have arisen in the subjects in the Medication-only and Combined treatment arms, this discussion should take up most of the CSPP teleconference.

Order of reporting: Sites will report in alphabetical order, with each site rotating to the first position on a weekly basis.

Decisions: Since the decision to make changes in a patient's medication regimen rests at the site level, no decisions regarding medication management will be made by the CSPP. Rather, the CSPP will serve as a vehicle for developing a common medication management culture and thereby will reduce cross-site variability.

ASAP: An exception to this rule occurs when the CSPP discussion suggests that ASAP procedures should be invoked to decrease the likelihood of subject attrition and/or to further explore/manage medication side effects. For example, the CSPP may recommend that a site meet with a patient/parent more frequently to exclude the possibility of emergent mania.

6.12 Procedures for Gathering Data for CSPP

The PTM includes defined circumstances under which the child's medication dose may be adjusted. With the exception of minor changes in timing of medication administration and protocol-driven upward adjustment in dose, alterations in a patient's medication regimen due to side effects will be reviewed with the site pharmacotherapy supervisor. If necessary, discussion of how best to present the information on the CSPP call will ensue. Site profiles for changes in medications will be discussed by the Cross-Site Pharmacology Panel (CSPP).

The Medication Count Log includes the following information: past medication dose and timing of administration, change since the last visit and why (scheduled, clinical circumstances or side effect driven), the identity of the reporter of the event, context of the report (phone call or regular appointment), checks on compliance, a short clinical note and the current FLX dose and timing of administration.

The Adverse Event Form (AEF) and Patient Safety Monitoring Form (PSMF) include information regarding adverse events of all type, including rating of relatedness to medication in those subjects assigned to pills conditions.

7.0 Pharmacotherapist Factors

7.1 Pharmacotherapist Experience

It is essential that pharmacotherapists have sufficient experience with the use of medications for MDD in adolescents to have an appreciation for the importance of adequate dosage as a condition for maximal therapeutic response. Pharmacotherapists should also be familiar with the relative medical importance of side effects associated with fluoxetine in particular and SSRIs in general and methods for their management. A background of knowledge about, and clinical experience in, the use of pharmacotherapy with fluoxetine (as well as other serotonin reuptake inhibitors, such as clomipramine, paroxetine, sertraline, citalopram and fluvoxamine) 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. Notably, in adult studies of treatment-resistant depression, failure to respond to pharmacotherapy combined with supportive psychotherapy have been strongly associated with failure to receive an adequate trial of 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 can be attributed to insufficient information about side effects or about the course of therapeutic effect. Hence, an excellent therapeutic alliance based in part on provision of adequate information to the patient and his or parents is an important part of the pharmacotherapist role.

To insure adequate experience by the pharmacotherapist, four criteria for participating in TADS as a pharmacotherapist must be met:

1. An MD, PA or RNP licensed to practice by the state in which the site resides.
2. At least one post-residency year of experience.
3. At least one year of working predominately with children and adolescents.
4. Experience in the pharmacotherapy of adult or pediatric depressive disorders.

These criteria, which will be monitored as part of pharmacotherapist certification, are to a large extent analogous to those instantiated for the CBT arm of the study and insure a fair test of the relative benefits of the treatments alone and in combination.

Each site will have a PT Supervisor, who will be certified by the Coordinating Center using procedures spelled out in the TADS Quality Assurance (QA Manual). The PT supervisor and the CC will monitor site pharmacotherapists according to QA procedures outlined in the QA Manual, which include the following:

- Review of the PTM
- A PT certification test
- Tape review of PT sessions
- Weekly PT supervision

7.2 Role of Pharmacotherapist:

Of critical importance is the pharmacotherapist's role as physician with primary clinical responsibility for the patient assigned to the medication alone condition. (Patients in COMB will have their CBT therapist as the primary clinician.) The pharmacotherapist should function as the patient's physician just as a physician would in a non-research clinical setting. Pharmacotherapists should not be permitted to alter the study design or amend research procedures; however, their role as members of a research team should not be allowed to interfere with their 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 PTM. In order to engage the patient rapidly in a positive relationship and inspire confidence in the treatment condition, pharmacotherapists should create an ambiance 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 depression and related disorders. Any tendency to administer the pharmacotherapy condition mechanically, to maintain inappropriate distance, or to relate in a perfunctory way is counter-therapeutic and must be avoided. The rationalization of anti-therapeutic 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 PTM. 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 pharmacotherapist, given the study constraints on active psychotherapeutic intervention.

7.3 Interpersonal processes:

Since some psychotherapies have been shown to affect treatment outcome in Major Depressive Disorder, it is important to maintain a specific pharmacotherapy approach as purely as possible while at the same time assuring the maximum possible therapeutic effect. 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 CBT condition. In order to avoid potential overlap between the PT and CBT conditions, it is necessary to specify the permitted and desirable elements of the interpersonal process in the pharmacotherapy condition as well as those that are prohibited.

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

To summarize, it is important that the prohibition of active psychotherapeutic intervention by the pharmacotherapist 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. Clinically indicated and appropriate supportive psychotherapeutic measures and interventions are sanctioned, whereas interventions related to specific organized systems of psychotherapy are not permitted.

8.0 Approved and Prohibited Actions:

The following sections define several areas of interpersonal process and types of intervention that are permitted within the context of the PTM and several that are not. These pertain to both pharmacotherapists and CBT therapists and (as noted above) require that both types of therapist be familiar with their respective treatment protocols.

8.1 Interpersonal context factors:

Major Depressive Disorder is an illness in which the patient may have negative expectations regarding the treatment intervention and outcome. Because of this, it is critically important to elicit the patient’s degree of 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 jitteriness or nausea. 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.

8.2 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 stage 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 depression. Furthermore, the patient may need special reassurance in the face of criticism of medication use by relatives or friends.

8.2a Psychological support of caregivers:

It is important to provide a general sense of caring and support to parents or other caregivers throughout the study by being empathic about current difficulties yet optimistic about the possibility of change. The primary available intervention is assurance that medication can help and that acute crises need not mean that a patient is failing to respond to treatment.

8.2b Psychological support of subjects:

Patients in the study may have doubts about taking drugs, especially if they are being teased at home or at school. Assuring them that they are not “weird” because they need to take a “drug” and correcting possible misperceptions about what the medication is doing may be helpful without entailing any special psychosocial treatment. It is perfectly appropriate, even necessary, for the pharmacotherapist to discuss with the patient (and parents, if needed) whether and how to inform significant others (such as friends or teachers) about the medication in particular and the research program in general.

8.3 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 Major Depressive Disorder. In addition, there should be some discussion of the notion that depressive symptoms may be related to abnormalities in brain or body biochemistry which the medication may help correct. Symptoms of Major Depressive Disorder and the side effects of the medication should also be discussed.

8.4 Advice:

Frequently, patients will ask what they can do to help themselves overcome Major Depressive Disorder. The pharmacotherapist should provide general encouragement to resist depressive symptoms as best they can while pointing out that medication should make this easier. Patients may also request advice concerning whether or not to make decisions or to attempt to engage in certain activities. Often, caregivers will solicit advice about how to handle a particular problem with their patient. General suggestions that they would be apt to receive from a primary care physician in the course of a brief office visit is acceptable; detailed recommendations about specific interventions or recommendations for reading materials where parents can learn how to do such interventions are not. For example, parents might be told to give firm clear commands but should not be shown how to establish a behavior modification program or to institute a behavioral contracting procedure. If the family is in a crisis that may compromise their ability to remain in the study, ASAP procedures should be invoked. In summary, simple advice not based in principles of social learning theory as specifically applied to MDD is permitted within the context of the PTM. Pharmacotherapists should briefly note any such direct advice in the clinical record.

8.5 Ventilation:

Patients will usually need to describe their symptoms. Within the limited time frame of the PTM 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.

8.6 Prohibited Actions:

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

1. Other than routine suggestions regarding (1) normal sleep hygiene or (2) management of FLX side effects, such as stomach aches, that might overlap with MDD symptoms, focusing on psychosocial change strategies targeting any of the MDD symptoms elicited during the scripted ADS review.
2. Focusing on specific psychological themes, especially those associated with antecedent negative events, interpersonal relationship problems and cognitive distortions, including but not limited to those associated with negative automatic thoughts.
3. Interpretations relating to psychological mechanisms of depression or anxiety.
4. Interpretation of the patient's feelings toward others or toward the therapist.
5. Specific behavioral instructions or routines.
6. Stress management or reduction interventions.
7. Recurrent focus of specific psychological themes of either the subject or the caregivers.
8. Explicit exploration with caregivers of systematic, organized behavioral programs.
9. Recommendation of reading materials or other resources likely to lead caregivers to adopt strategies similar to those employed in other arms of the study.
10. Changes in school programming either through direct interaction with the teacher or indirect guidance to parents.
11. Strong interpersonal involvement with either subject or parents, including meetings beyond those prescribed in the study protocol.

Appendix A. List of Drug Classes for Inclusion or Exclusion of Subjects*

Drug Class	If Episodic Use	If Chronic Use
Anorexics	N	N
Antacids	Y	Y
Antiarrhythmics	N	N
Anti-asthma agents		
Systemic, ventilator	Y	Y
Topical	Y	Y
Intal inhaler	Y	Y
Antibiotics	Y	Y
Anticoagulants	N	N
Anti-diarrheas	Y	N
Antihistamines for allergies (non-selective or selective H1 antagonists)	Y	Y
Anti-hypertensives	N	N
Anti-nauseants	Y	N
Anti-seizure medications	N	N
Aspirin	Y	Y
Birth Control (e.g., BCP, Norplant, Depo-Provera)	Y	Y
Cough/Cold preparations	Y	N
Diuretics	N	N
H2 blockers (e.g., anti-ulcer meds)	Y	Y
Herbal remedies for depression (e.g. St. John's Wort)	N	N
Hormones (other than BCPs)	Y	N
Hypoglycemic agents	N	N
Insulin	N	Y
Laxatives	Y	Y
Narcotics	Y	N
Non-narcotic analgesics	Y	Y
Sedative-Hypnotics	Y	N
Melatonin	Y	Y
Trazodone	Y	Y
Chloral hydrate	Y	N
Diphenhydramine (e.g. Tylenol PM)	Y	N
Benzodiazepines	N	N
Zolpidem (Ambien)	Y	N
Steroids	Y	Y*
NSAIDS	Y	Y
Tryptophan	N	N

***Note that this list does not include psychotropic medications, specifically excluded in the in/exclusion criteria.**

**** If taken before study initiation for a non-mental health indication and dose is stabilized:**

Y = subject may be included in study and/or medication may be used during treatment in which case it will be recorded on the CML.

N = subject must be excluded from the study before randomization. Use documented after randomization or, if problematic with respect to study treatments, managed according to ASAP and/or early termination procedures.