PROCEDURES FOR MANAGING PREGNANCY RISK IN THE NIMH TREATMENT OF ADOLESCENT DEPRESSION STUDY (TADS)

Contact: John S. March, M.D.
Department of Child and Adolescent Psychiatry
Department of Psychology – Soc & HLTH
718 Rutherford St Durham, NC 27705
Box 3527 Med Ctr Durham, NC 27710
(p) 1-919-416-2404
(f) 1-919-416-2420
jsmarch@acpub.duke.edu

I. Rationale

In a study of teenagers with depression where pregnancy is an absolute exclusion criterion before randomization and an important consideration post-randomization, it is necessary to delineate specific procedures for managing pregnancy risk that may arise during TADS. **All TADS clinical staff are expected to be familiar with the *TADS Pregnancy Risk Management Manual and procedures.***

II. Relationship to Adverse Event Monitoring

Procedures for recording pregnancy fall within the general area of AE/ASAP reporting. By definition, pregnancy when it occurs will be managed and documented via ASAP procedures. This manual supplements the TADS AE/ASAP Manual, which specifies types and indications for AE/SAE/ASAP reporting only one of which involves pregnancy. When pregnancy triggers ASAP, the reason for ASAP referral, the decision of the ASAP Panel and the outcome of the ASAP intervention will be recorded on the ASAP Form. Pregnancy itself is not a severe adverse event (SAE); however, when pregnancy triggers a SAE—for example, a suicide attempt leading to medical hospitalization—the SAE form also should be completed.

III. Pre-Randomization Procedures

Pregnancy is an absolute exclusion criterion. All subjects must have a negative urine or serum pregnancy test (the choice of test is at site IRB discretion) prior to randomization. Sexually active girls must consent to use of effective birth control in order to participate. Effective birth control is defined as use of the birth control pill, an IUD or barrier methods preferably in combination with a spermicidal foam or suppository. Pre-randomization pregnancy risk in TADS is managed as follows:

During the Assent/Consent procedure, there is an initial statement that pregnancy is an exclusion. The RISK section the addresses the risk of pregnancy in more detail:

- the drug treatment used in TADS may not be healthy for the fetus
- a pregnancy test is needed before starting the study
- proven contraception must be used if sexually active
- pregnancy will result in being dropped from the medication portion of the trial

During the Gate C2 visit prior to disclosure of randomization status, confidentiality procedures are reviewed, including for females assigned to any TADS treatment:

- need to track menstrual cycle
- missed period will prompt therapist to ask about pregnancy
- disclosure will be managed per state law/ IRB defined procedures
- procedures for tracking menstrual cycles

IV. Routine Monitoring for Pregnancy Risk

Clinical Assessment

At every office during Stages I, II and III, it is expected that the primary study pharmacotherapist will inquire about pregnancy risk. CBT therapists are not expected to inquire about pregnancy risk unless clinical circumstances dictate.

During Stage IV, routine monitoring of pregnancy risk is not done as patients have ended the treatment portion of TADS.

Tracking Forms for Monitoring Suicidality

In addition to AE/ASAP forms, TADS includes a specific form for monitoring menstrual cycles in female subjects. Specifically, either non-clinical (e.g. study coordinator) or clinical staff (e.g. primary clinician) is expected to track the Female Menstrual Cycle (FMC) form used to monitor menstrual cycles across time in female patients. **Site management at the Coordinating Center will work with the study coordinator at each site to identify the designated individual at each site who is responsible for tracking the FMC.** Clinical follow-up with the primary study clinician is evoked when data from the FMC is missing (due to a missed assessment visit or information left blank) or when information provided by the patient on the FMC or within clinical sessions raises a "red" flag (e.g., late menstrual cycle, sexual activity reported).

V. Information Provided to Teen, Primary Caregiver and Doctor

For patients taking fluoxetine, patients, their primary caregivers and, if desired, their primary care and/or obstetrician should be informed that current research regarding the risk of fluoxetine during pregnancy suggests the following:

- Fluoxetine does not increase the risk for intrauterine fetal death or major birth defects.
- Fluoxetine does not increase the risk for impairment in prenatal growth or birth weight in infant born to mothers taking fluoxetine. Major depression can cause women to lose weight and it is possible that an undertreated mood disorder, and not the drug itself, could affect the weight of both mother and baby. Thus, as is usual practice, doctors should monitor weight gain carefully in pregnant women being treated with antidepressants.
- Children who are prenatally exposed to fluoxetine show no differences in cognitive function, temperament and general behavior compared with children who were not exposed.
- Withdrawal symptoms, including transient jerky movements and seizures, rapid heart beat, irritability, feeding difficulties and profuse sweating, cab occur in some newborns whose mothers were treated with antidepressants near the end of the pregnancy. Such symptoms are more common with tricyclic antidepressants that with fluoxetine, but can occur with SSRIs. Thus, physicians should consider tapering to a lower dosage or discontinuing fluoxetine 10 to 14 days before the due date, resuming treatment again after delivery if warranted.
- How a teen responds to pregnancy is related to her early childhood experiences, coping mechanisms, personality style, psychological functioning, life situation (including social support network), and physical status. In some teens, pregnancy itself can lead to problem behaviors, including failure to seek medical care, substance use and dropping out of school, as well as negative emotional states. In turn, these pose a risk not only to the teen but to the unborn child. Importantly, depression can increase the risk for poor behavioral and pregnancy outcomes both before and after delivery. Thus, when a teen and her physician considers the benefits versus the risks of drug therapy during pregnancy, it is important to note that the risks of depression (for example, being suicidal, not eating properly or enough) can do more harm to a pregnancy or fetus than fluoxetine.

References

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VI. TADS Interventions and Procedures

As with suicide risk, three general principles must apply to all interventions made in the management of pregnancy during TADS: (1) the teen's safety and the safety of the fetus are the paramount consideration; (2) continuing TADS treatment is only appropriate if it contributes in a meaningful way to the child's clinical care, does not conflict with other necessary interventions, and is consistent with the rules for managing pregnancy risk outlined below; and (3), other interventions relevant to pregnancy management within or outside the TADS protocol must be implemented if clinically appropriate.

With this in mind, the procedures when pregnancy is disclosed or discovered in TADS are:

1. Within the framework permitted by state law and IRB procedures, disclosure to parents or designated primary caregiver is mandatory. Typically, this would be accomplished within the ASAP framework.
2. In patients assigned to "pills only" during stage I premature termination via ASAP is mandatory to allow breaking the blind to determine whether the patient is taking fluoxetine or PBO. Since patients are then referred to an outside treatment provider, the decision regarding whether to initiate, terminate, continue or adjust treatment with fluoxetine or any other medication is left to the patient and her doctor. Patients assigned to PBO are eligible for CBT per usual TADS procedures.
3. In patients assigned to fluoxetine during Stage II or III premature termination via ASAP also is mandatory. Since patients are then referred to an outside treatment provider, the decision regarding whether to terminate, continue or adjust treatment with fluoxetine is left to the patient and her doctor.
4. In patients assigned to COMB, premature termination is not necessary. However, to remain in TADS treatment, treatment with fluoxetine must be discontinued and CBT continued. In this instance, we are assuming voluntary discontinuation of fluoxetine consistent with prior informed consent. Since the team is not directly discontinuing the drug, this definition is not counter to our definition of Premature Termination. A patient wishing to continue fluoxetine while pregnant exits the study treatment portion via ASAP as a treatment dropout.
5. In patient assigned to CBT, TADS continues unchanged.

VII. Summary

This manual provides a consistent vehicle for sites to handle situations involving pregnancy risk prior to randomization and pregnancy during TADS. Since this treatment study is being conducted

at 12 different sites, it is important that there be consistency and agreement in the manner in which these situations are handled, so as not to bias treatment results or to invite site-by-treatment interactions. Above all, this manual is intended to provide compassionate and competent care to teens and their families in TADS so that risk to the patient is minimized and the benefits of treatment from TADS or though ASAP procedures can be maximized.