

# Investigator Presentation: Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT): Constantine Lyketsos, M.D

**JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE**

February 16-18, 2005, Hilton Gaithersburg, 620 Perry Parkway, Gaithersburg, Maryland.

Highlights.....	1
Presentation Text.....	4
Presentation Slides .....	9

## Highlights

- **DR. LYKETSOS IS STEERING COMMITTEE MEMBER:** He and his colleague Dr. Piantadosi (who is in the audience) are both on the steering committee of the ADAPT trial.
- **ALZHEIMER'S AFFECTS 4+ MILLION PEOPLE IN US:** Alzheimer's disease affects 4-4.5 million people in the US and this number may increase with the expected aging of the population to 12-15 million people. Observational studies suggest "substantial reductions of risk of Alzheimer's disease" with NSAIDs.

## PREPARED STATEMENT:

- **TREATMENTS SUSPENDED ON 12-17-04:** The ADAPT study steering committee suspended the NSAID treatments on December 17, 2004.
- **MISUNDERSTANDING ABOUT SUSPENSION:** There "is much public misunderstanding about our decisions and their rationale".
- **RISK: BENEFIT BALANCE IS DIFFERENT IN PREVENTION TRIALS:** The risk:benefit balance is different in a prevention trial from a treatment trial because "risks are typically not balanced by any promise of tangible near-term benefit".
- **SAFETY ANALYSIS NOT YET AVAILABLE:** Auditing and tabulation of the ADAPT trial's cardiovascular safety data is not "quite completed" so that he cannot present the trial safety results today.
- **UNUSUAL CIRCUMSTANCES: DATA NOT SUFFICIENT TO SUSPEND: EXTERNAL DATA**

**RAISED CONCERNS ABOUT TRIAL “PRACTICALITIES”:**

“For today, we note that, even with the risk:benefit calculus of a prevention trial, these data would not, in themselves, have led to our decision to suspend either treatment. In reality, those decisions were made in very unusual circumstances. They reflected events external to ADAPT that raised strong concerns about the practicalities of continuing the treatments”.

- **ADAPT TRIAL DESIGN:** The ADAPT trial is a double blind trial of celecoxib 200 mg bid, naproxen 220 mg bid, and placebo in subjects at least 70 years of age in the prevention of Alzheimer’s dementia and age-related cognitive decline. Subjects with “preexisting uncontrolled hypertension, anemia or a history of gastrointestinal bleeding, perforation or obstruction” were excluded.
- **DATA SAFETY MONITORING BOARD:** The ADAPT DSMB (ADAPT calls this the “TEMC”) meets twice a year. In addition “the ADAPT study officers and consultants also conduct reviews of safety data at intervals between TEMC meetings”. Dr. Bruce Psaty “a physician with expertise in evaluation of cardiovascular risks in clinical trials” was recently added to the DSMB. The ADAPT study officers had been “relatively reassured” by the “periodic reviews of the celecoxib safety data” and the “study chair communicated this information in a telephone conversation on 15 October 2004 with Dr. Sharon Hertz at FDA”.
- **DSMB TOLD 12-10-04 OF WEAK NAPROXEN SIGNAL BUT**

**TREATMENTS CONTINUED:**

Analyses of the available data (in 2,528 subjects with average duration of 20 months) were presented to the TEMC on December 10, 2004, and “suggested a weak signal suggesting increased risks of cardiovascular and cerebrovascular events with naproxen. Reviewing the data, however, we understood well the TEMC's evident conclusion that this signal was not sufficiently compelling or definitive to warrant a recommendation to suspend the treatment or to otherwise alter the protocol”.

- **TREATMENTS SUSPENDED ON 12-17-04, THE SAME DAY CELECOXIB APC RESULTS RELEASED:** On December 17, 2004, the APC and PreSAP trials were suspended because of “increased cardiovascular risks” in the APC trial.
- **BASIS FOR TREATMENT SUSPENSION:** The news of the APC results “led to extensive discussion among the steering committee on that day centering on the following considerations .... one arm of the APC trial had used the same celecoxib dosing as ADAPT, 200 milligrams twice daily, but over a longer period of time. News reports cited a relative risk of 2.5 for cardiac events in this arm of APC. Although this risk was reported as only ‘marginally significant,’ a greater cardiac-risk signal was reported with the higher APC dosage of 400 milligrams twice daily. Thus, we took seriously the possibility of harm over time to ADAPT participants receiving celecoxib. Especially in a prevention trial with no strong prospects of immediate benefit, we

had strong misgivings about continuing celecoxib treatments”.

- **CELECOXIB CONTINUATION WOULD HAVE NEEDED CONCURRENCE OF IRBs:** If they had “discounted the APC data and continued celecoxib .... we would clearly have needed the concurrence of the seven IRBs that oversee ADAPT. These IRBs began almost immediately to question us about implications of the APC results and seemed likely to question a decision to continue. Even if we had persuaded them to permit continuation of celecoxib using a revised consent process, we would surely be involved in lengthy discussions with these IRBs. In the meantime, we would be unable to offer much explanation to our participants, thereby endangering the relationship of trust that is vital to the success of long-term trials.”
- **EXPECTED INCREASE IN DROPOUTS FOLLOWING APC RESULTS:** “Number three” on the list of concerns was that “ADAPT was experiencing some difficulty with adherence to treatments” following the Vioxx withdrawal and they “expected the announcement of the APC results to exaggerate the problem further with scores of participants stopping treatment...”. “Thus, even though the ADAPT safety data did not, themselves, warrant suspension of celecoxib treatments. There seemed little practical choice but to do so.”
- **NAPROXEN CARDIAC SAFETY WAS “CONCERNING”:** “We next confronted the dilemma of what to do about naproxen and its placebo. The “accumulated naproxen safety data” was “somewhat more

concerning than the celecoxib safety data”. Some “post hoc data composites barely reached statistical significance .... for naproxen versus placebo” but “no singular vascular event was clearly more frequent with naproxen versus placebo.”

- **CHANGE TO TRIAL OF ONLY NAPROXEN AND PLACEBO COULD CONFUSE SUBJECTS:** They could have revised ADAPT to “a two-armed trial of naproxen versus placebo” but subjects “might end up getting confused and taking the wrong pills and many would stop taking their treatments altogether.”
- **“NOTABLE” INCREASE IN GI BLEEDING WITH NAPROXEN:** In addition, this would have given the “misleading” impression that the ADAPT data suggested that “celecoxib was risky but naproxen was ‘safe’ ”. In fact, even though they attempted to reduce the G.I. risk of naproxen “by excluding participants with prominent risk factors other than age, the ADAPT data showed a notable increase in G.I. bleeding with naproxen versus placebo.”
- **TOTALITY OF ARGUMENTS RESULTED IN SUSPENSION DECISION:** “Especially amid concerns that ADAPT was exposing its participants to potential risks that were immediate, while the trial's hoped-for benefits lay in the future, the totality of the above arguments lead the steering committee to suspend both treatments and to also suspend enrollment into ADAPT.”
- **PAPER TO BE SUBMITTED FOR PUBLICATION IN FEW WEEKS: WILL NOT HAVE FULL SAFETY ANALYSIS:** They “expect, within a few weeks, to

submit a scientific paper for peer review and publication. The paper's focus will be on the process and rationale underlying the decision to suspend treatments and enrollment in ADAPT. Because these decisions did rely, in some measure, on the ADAPT safety data as of 10 December, the paper will, also, disclose some of these data.”

- **FOLLOW-UP OF SUBJECTS AND EVENT CLARIFICATION/ADJUDICATION IS PLANNED:** Subjects in the ADAPT study will have “a further two years of additional safety monitoring”. In addition, additional information will be collected on some of the adverse events, and “all information” will be submitted for “expert adjudication”.

## Presentation Text

Good morning, everyone. I do not have slides. My name is Constantine Lyketsos. I am a professor at Hopkins and I am presenting here today on behalf of the ADAPT study, Alzheimer's Disease Anti-inflammatory Prevention Trial. I would like to thank the committee for inviting us to present. I am here today with my colleague, Steve Piantadosi, who is also on the steering committee and will be available to answer any questions that might come up later on as well.

I have a prepared statement that will be distributed to the committee later on today. I delivered it to the staff this morning as I was arriving.

Before I get into the statement, I just wanted to take a few moments to remind us of the public-health importance of Alzheimer's disease to somewhat set the context about how the ADAPT trial has started specifically. Alzheimer's, as we all know, is a major public-health problem. It is a devastating disease, typically runs a ten-year course of neurodegeneration affecting probably close to 4 or 4-and-a-half million of our citizens at present and the number is

expected to rise given the aging of the population of the next several decades to approach, perhaps, 12 to 15 million, based on current projections.

Because of these public-health numbers, there has been a very significant effort in our field for the last several years to develop preventive strategies for Alzheimer's disease because, once neuronal degeneration has started, the evidence that treatments work, so far, is very weak.

These preventive strategies have centered on several possible treatments but the most supported by the observational literature have been non-steroidals with over 24 studies right now including four prospective population studies suggesting substantial reductions of risk of Alzheimer's disease perhaps with risk ratios, in some cases, as much as 0.4 or 0.5. So it is within that context that ADAPT was started with the support of the National Institute of Aging.

I will move now to reading the prepared statement.

*The steering committee of the ADAPT study welcomes the opportunity to present the rationale for its decision, on December 17, 2004, to suspend the NSAID treatments in ADAPT. This presentation is important because there is much public misunderstanding about our decisions and their rationale.*

*The ADAPT Steering Committee is deeply committed to the safety of human subjects, even more so in the context of prevention trials where risks are typically not balanced by any promise of tangible near-term benefit. In this notable way, prevention trials differ from treatment trials whose participants may hope for relief of symptoms or improved outcomes in a condition already diagnosed.*

*The risk:benefit balance in prevention trials is even further removed from a comparison of the benefits of a proven treatment with its acknowledged risks. Because ADAPT has not quite completed the process of auditing and tabulating the trial's cardiovascular safety on the date of suspension, we cannot, today, present the trial safety results at the time of the decision to suspend.*

*We defer that presentation to a peer-reviewed publication planned for the near future. For today, we note that, even with the risk:benefit calculus of a prevention trial, these data would not, in themselves, have led to our decision to suspend either treatment. In reality, those decisions were made in very unusual circumstances. They reflected events external to ADAPT that raised strong concerns about the practicalities of continuing the treatments.*

*As the advisory committee probably knows, ADAPT is a randomized, double-masked, multicenter trial of celecoxib, 200 milligrams twice daily, or naproxen sodium 220 milligrams twice daily versus placebo for the primary prevention of Alzheimer's dementia and for the prevention of age-related cognitive decline which is, in many instances, a prodrome of Alzheimer's disease.*

*ADAPT also provides an opportunity to study the long-term safety of its treatments in a healthy elderly population. Eligibility criteria include an age of 70 years or older at enrollment and a health history that excludes many of the known risk factor for adverse events with NSAID treatments; for example, we exclude those with preexisting uncontrolled hypertension, anemia or a history of gastrointestinal bleeding, perforation or obstruction.*

*To provide independent recommendations regarding continuation of the trial, the ADAPT Treatment Effects Monitoring Committee, or TEMC, which, I suppose, is our term for a DSMB, meets twice a year. In response to emerging concerns about cardiovascular risks with NSAIDs, membership of the TEMC was recently expanded to include Dr. Bruce Psaty, a physician with expertise in evaluation of cardiovascular risks in clinical trials.*

*As an additional safeguard for participant safety, the ADAPT study officers and consultants also conduct reviews of safety data at intervals between TEMC meetings. Amid the emerging controversy about the cardiovascular safety of selective COX-2 inhibitors, the ADAPT study officers had*

*been relatively reassured by their periodic reviews of the celecoxib safety data. The study chair communicated this information in a telephone conversation on 15 October 2004 with Dr. Sharon Hertz at FDA.*

*As of December 17, 2004, the date of suspension of treatments and enrollment in ADAPT, we had enrolled 2,528 participants. Of these, 2,463 had been randomized before October 1 of '04 with some 20 months average duration of observation. These participants contributed a total of 3,888 person years of follow up to analyses that were presented to the TEMC on December 10, 2004.*

*Those analyses suggested a weak signal suggesting increased risks of cardiovascular and cerebrovascular events with naproxen. Reviewing the data, however, we understood well the TEMC's evident conclusion that this signal was not sufficiently compelling or definitive to warrant a recommendation to suspend the treatment or to otherwise alter the protocol. This was on December 10, 2004.*

*Thus, the study officers were surprised on December 17 by announcements that two trials of celecoxib for the prevention of recurrent adenomatous colon polyps had been suspended citing increased cardiovascular risks with treatment in one of these studies, the Adenoma Prevention with Celecoxib trial, or APC. This news led to extensive discussion among the steering committee on that day centering on the following considerations.*

*Number one; one arm of the APC trial had used the same celecoxib dosing as*

*ADAPT, 200 milligrams twice daily, but over a longer period of time. News reports cited a relative risk of 2.5 for cardiac events in this arm of APC. Although this risk was reported as only "marginally significant," a greater cardiac-risk signal was reported with the higher APC dosage of 400 milligrams twice daily.*

*Thus, we took seriously the possibility of harm over time to ADAPT participants receiving celecoxib. Especially in a prevention trial with no strong prospects of immediate benefit, we had strong misgivings about continuing celecoxib treatments.*

*Knowing almost nothing at the time about the particulars of the APC trial and, in light of the apparent lack of risk with celecoxib in the other prevention trial, we might have discounted the APC data and continued celecoxib. To do so, however, we would clearly have needed the concurrence of the seven IRBs that oversee ADAPT. These IRBs began almost immediately to question us about implications of the APC results and seemed likely to question a decision to continue.*

*Even if we had persuaded them to permit continuation of celecoxib using a revised consent process, we would surely be involved in lengthy discussions with these IRBs. In the meantime, we would be unable to offer much explanation to our participants, thereby endangering the relationship of trust that is vital to the success of long-term trials.*

*Number three; as is common in long-term trials, ADAPT was experiencing some difficulty with adherence to treatments. This difficulty grew*

*following the withdrawal of rofecoxib and we expected the announcement of the APC results to exaggerate the problem further with scores of participants stopping treatment, in effect, "voting with their feet." This would erode statistical power and increase the potential for bias in ADAPT.*

*Thus, even though the ADAPT safety data did not, themselves, warrant suspension of celecoxib treatments. There seemed little practical choice but to do so.*

*We next confronted the dilemma of what to do about naproxen and its placebo. As suggested above, we regarded the accumulated naproxen safety data as being somewhat more concerning than the celecoxib safety data. Yet, they, also, were not compelling. Although some post hoc data composites barely reached statistical significance--these are post hoc data composites barely reached statistical significance for naproxen versus placebo, no singular vascular event was clearly more frequent with naproxen versus placebo.*

*Furthermore, vascular risks were not expected with naproxen treatment. In fact, a substantial body of prior data at the time had suggested that naproxen offers some cardiovascular protection. This lack of prior expectation cast further doubt on the meaning of the naproxen data in ADAPT which were vulnerable, in any case, to the problem of multiple comparisons.*

*We could, therefore, have attempted to have revised ADAPT to a two-armed trial of naproxen versus placebo, instructing our participant to stop taking*

*their "white pills," as they are known in the study, which are celecoxib and its placebo, but continue to take their "blue pills," which contain naproxen and its placebo.*

*However the dangers were several. Participants might end up getting confused and taking the wrong pills and many would stop taking their treatments altogether. We faced an ethical dilemma. The suspension of celecoxib and continuation of naproxen would have created the impression among participants and among the general public that celecoxib was risky but naproxen was "safe." At least based on the signals from the ADAPT data, this impression would have been misleading.*

*What would we then tell participants about the risks with naproxen as we led through the inevitable process of revised consent necessitated by the protocol revision? Would the multiplicity of IRBs even allow us to follow this course?*

*Finally, there was another risk to consider. We began ADAPT expecting to see some increase with naproxen in gastrointestinal bleeding and other events. Even though we attempted to reduce these excess G.I. risks by excluding participants with prominent risk factors other than age, the ADAPT data showed a notable increase in G.I. bleeding with naproxen versus placebo.*

*Especially amid concerns that ADAPT was exposing its participants to potential risks that were immediate, while the trial's hoped-for benefits lay in the future, the totality of the above arguments lead the steering committee to suspend both treatments and to also suspend enrollment into ADAPT.*

*As noted above, we expect, within a few weeks, to submit a scientific paper for peer review and publication. The paper's focus will be on the process and rationale underlying the decision to suspend treatments and enrollment in ADAPT. Because these decisions did rely, in some measure, on the ADAPT safety data as of 10 December, the paper will, also, disclose some of these data.*

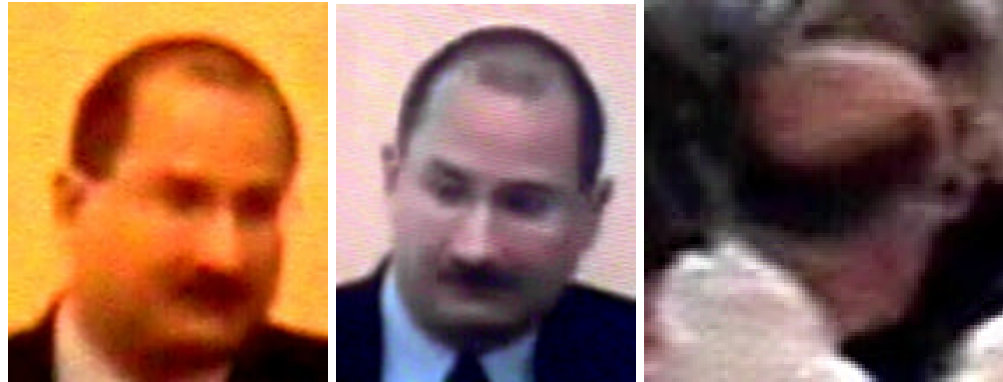
*We are also cooperating with ongoing efforts at the NIH to investigate the cardiovascular and cerebrovascular risks of NSAIDs. In addition, the NIA and the ADAPT Steering Committee are committed to a further two years of additional safety monitoring of our participants.*

*In preparation for a later, more definitive discussion of the ADAPT safety data, we plan to revisit a number of the adverse events to collect additional information and then to submit all information available now or later to a process of expert adjudication. Depending on particulars, the latter process will take months. In the nearer term, we concur with the expert opinion that, having taken these widely publicized decisions, the steering committee must fulfill its obligation to disclose its reasons for doing so based upon the data available.*

*At the same time, we are intent that our public presentation even of the current "working" data must be at the highest attainable standards of accuracy.*

Thank you.

## Presentation Slides



Only a verbal presentation was made. It was stated that the study was stopped for practical reasons and not because of a suggestive signal of increased cardiovascular toxicity with naproxen. Considerable discussion ensued about stopping rules and about the need to keep knowledge of the data to data monitoring people alone and not to steering committee members.