Treatment of depression in children and adolescents
Neal D Ryan

Depressive disorders during youth occur frequently, are chronic and recurrent, and are associated with significant functional impairment, morbidity, and mortality. Two psychotherapeutic approaches—cognitive behavioural therapy and interpersonal therapy—are each better than wait-list or treatment-as-usual approaches. Several antidepressants have proven efficacious compared with placebo; however, more than half the studies comparing antidepressant treatment with placebo in children and adolescents with depression have not shown any benefit of the active compounds. Suicide rates are decreasing overall in adolescents, and there seems to be a correlation between the use of selective serotonin reuptake inhibitors (SSRIs) and a decrease in completed suicide. However, there was a signal for increase in suicide attempts and suicidal ideation in patients on acute antidepressant treatment when all antidepressants were assessed as a single group. Thus, there is substantial debate about the best approach to treat this serious disorder. Here, we discuss the treatment options for depression in children and adolescents.

Major depressive disorder is common during childhood with an estimated point prevalence of about 1–2% in school-age children (6–12 years) and 2–5% in adolescents (13–18 years), with 14–25% of youths experiencing at least one episode of major depression before adulthood. Depression has been suggested to be more frequent in the past few decades than earlier in the 20th century, paralleling a secular increase in mild and moderate depression in adults. In most youths, the episode of major depression recurs within 5 years. The disorder is frequently comorbid with anxiety disorders, dysthymia, disruptive disorders, or substance abuse and is associated with increased risk for early pregnancy. With adolescence the sex ratio changes from approximately equal frequency in boys and girls before puberty to about a two to one excess in girls. This increase in the absolute rate in girls is probably an overestimate because of issues of referral bias. Nevertheless, because bipolar disorder tends to have an onset early in life, whereas major depression can begin at any age, first episodes of depression early in life will precede eventual bipolar depression in youths, which includes: adult to child familial transmission and significantly heightened risk for depression in the adult relatives of depressed youths; twin studies of depressive symptoms and depressive disorder in youth, especially those using parents as informants, giving estimates of heritability of 40–80% (with one study giving a lower estimate); and twin studies using child informants, giving lower but still significant estimates of heritability. Environmental risk factors for child depression might only partly overlap risk factors for depression late in life. Specific child risk factors include perinatal insults, motor skill deficits, and caretaker instability.

Search strategy and selection criteria
We searched MEDLINE (2000–04) and used all material from the FDA web site. Search terms were “depressive disorder” and “childhood depression” in combination with a limit to patient age range of 6–18 years. We then limited the results using the terms “epidemiology”, “natural history”, and “treatment”. We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference list of articles identified by this search strategy and selected those we judged relevant. We sought advice from several experts in the field to help locate information on studies funded by pharmaceutical industries that have been presented at national meetings but not yet published. Several review articles were included because they provide excellent comprehensive overviews that exceed the scope of this Seminar.
disorder more frequently than first-onset depression later in life.

**Treatment studies**

There are far fewer treatment studies of depression in children and adolescents than in adults for reasons of patient availability (there are fewer children than adults and the point prevalence of depression is lower through much of childhood), funding availability (both industry and other funding sources fund fewer child studies than adult studies), and investigator availability. Therefore, the confidence intervals for deciding whether or not the efficacy of antidepressant treatments in youth is superior to that of placebo or whether particular side-effects (eg, suicidality) occur more frequently than with placebo are much wider—with fewer studies it is difficult to assess whether a treatment works or to pin down an important side-effect.

The US Food and Drug Administration (FDA) regulatory requirements have enormous effect on pharmaceutical industry drug-development strategies. To get an FDA indication for use of an antidepressant for a particular disorder and in a particular age group (eg, for children with depression) the FDA asks for two separate positive studies out of the studies industry chooses to complete. However, because the market for these agents in youth is small and because typically the compounds are tested in youth late (so the compounds are considered here), adolescents secondary endpoint measures are much wider—with the point prevalence of depression is lower through much of childhood). Therefore, assuming a particular compound works equally well in youth as in adult depression, the chances of obtaining an FDA indication for depression in youth are very much less since more than half of adult (and child/adolescent) antidepressant studies done in recent years have not produced a significant effect.

Studies of psychotherapy are difficult to compare with studies of pharmacotherapy in this disorder. Most psychotherapy studies have used wait-list or treatment-as-usual approaches for the control group rather than a control that would more fully control expectancy effects. All pharmacotherapy studies in child depression completed or ongoing have had placebo control groups, providing a higher bar for the pharmacological studies than for the psychotherapy studies.

Ultimately, current studies of the treatment efficacy of both psychotherapy and pharmacotherapy for depression in youth seem to be compatible with a

<table>
<thead>
<tr>
<th>Agent</th>
<th>Publication status</th>
<th>Sample characteristics</th>
<th>Results</th>
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<tbody>
<tr>
<td>Fluoxetine</td>
<td>Published, Simeon et al</td>
<td>Industry-funded, single-site, N=140, adolescents</td>
<td>No statistical difference between fluoxetine and placebo but had very high placebo response rate</td>
</tr>
<tr>
<td></td>
<td>Published, Emslie et al</td>
<td>Industry-funded, multi-site, N=165, children and adolescents</td>
<td>Fluoxetine superior to placebo on primary endpoints</td>
</tr>
<tr>
<td></td>
<td>Published, Emslie et al</td>
<td>Industry-funded, multi-site, N=219, children and adolescents</td>
<td>Primary endpoint, CDRS-R, did not show significant difference (p&lt;0.10) but all other endpoints significantly better for fluoxetine</td>
</tr>
<tr>
<td></td>
<td>Published, March et al (TADS group)</td>
<td>Industry-funded, multi-site, N=439 in four cells (placebo, CBT, fluoxetine, fluoxetine+CBT), adolescents</td>
<td>Fluoxetine-only group superior to placebo on one of two primary endpoints</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Published, Wagner et al</td>
<td>Pair of identical-methodology independent industry funded multi-site studies combined into one omnibus test, N=355, across both studies, children and adolescents</td>
<td>Neither study separately reached significance. When combined (preplanned), the overall aggregate found sertraline significantly better than placebo on primary endpoint</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Published, Wagner et al</td>
<td>Industry-funded, multi-site, N=174, children and adolescents</td>
<td>Citalopram significantly better than placebo on primary and secondary endpoints</td>
</tr>
<tr>
<td></td>
<td>Unpublished, some data available on FDA web site</td>
<td>Industry-funded, multi-site, N=244, adolescents</td>
<td>No indication of efficacy</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Published, Keller et al with additional data on GSK website</td>
<td>Industry-funded, multi-site, N=180 in paroxetine and placebo cells (with another 95 in an imipramine cell not further considered here), adolescents</td>
<td>Neither primary endpoint measure reached significance but paroxetine significantly better than placebo on four of six secondary endpoint measures</td>
</tr>
<tr>
<td></td>
<td>Unpublished, presented at scientific meeting, Emslie and data available on GSK web site</td>
<td>Industry-funded, multi-site, N=206, children and adolescents</td>
<td>No indication of efficacy</td>
</tr>
<tr>
<td></td>
<td>Unpublished, presented at scientific meeting, Milin and data available on GSK web site</td>
<td>Industry-funded, multi-site, N=286, adolescents</td>
<td>No indication of efficacy</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Unpublished, presented at scientific meeting, Wagner</td>
<td>Industry-funded, multi-site, N=264, children and adolescents</td>
<td>No indication of efficacy</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Unpublished, presented at scientific meeting, Emslie</td>
<td>Industry-funded, multi-site, N=165, children and adolescents</td>
<td>No indication of efficacy</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Published abstract only, Emslie et al</td>
<td>Industry-funded, multi-site, N=201, children and adolescents</td>
<td>Nefazodone superior on secondary outcome measure</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Unpublished, some data available on FDA web site</td>
<td>Industry-funded, multi-site, N=284, children and adolescents</td>
<td>No indication of efficacy</td>
</tr>
<tr>
<td></td>
<td>Unpublished, some data available on FDA web site</td>
<td>Industry-funded, multi-site, N=133, children and adolescents</td>
<td>No indication of efficacy</td>
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CDRS-R=children’s depression rating scale-revised; CBT=cognitive behavioural therapy.

**Table 1: Randomised controlled antidepressant trials with SSRIs and other third-generation antidepressants**
hypothesis that these treatments might work as well in youth as they do in adults. On the other hand, they might not. With the wide confidence intervals inherent in the small number of studies it is just too soon to say for sure.

Therefore, the question of how many data and what quality data are needed to ascertain efficacy or side-effects is challenging. Simply asking for the same data as needed for studies in adults leaves one, at present, with little in the way of treatment options.

**Psychotherapeutic treatment**

Both psychotherapeutic and pharmacological treatment studies of major depression through the lifespan are complicated by a relatively high placebo or non-specific treatment response rate, approaching 30% or more in many studies.

Cognitive behavioural therapy seems to be effective in the treatment of child and adolescent depression. Most psychotherapy studies of depression in youth have been comparisons of wait-list control (patients receive no treatment for the duration of the study, but are promised treatment at the end as a quid-pro-quo) and treatment-as-usual approaches that do not control for expectancy effects. The single exception is the study of Brent and colleagues, which showed superiority of cognitive behavioural therapy over two other reasonable psychotherapeutic approaches (family and supportive therapy) with good control for treatment contact amount and treatment expectancy.

In the TADS study, the only controlled study comparing psychotherapeutic and pharmacological approaches, cognitive behavioural therapy alone (43% response rate) was not superior to placebo (35% response rate) in any analysis, fluoxetine alone (61% response rate) was superior to cognitive behavioural therapy alone in both pre-planned analyses and was superior to placebo in one of the two analyses, and cognitive behavioural therapy plus a selective serotonin reuptake inhibitor (SSRI) (71% response rate) was superior to cognitive behavioural therapy alone and placebo alone in both analyses and slightly better than SSRI alone in one analysis. The reason for lack of efficacy of cognitive behavioural therapy alone in this study compared with the robust treatment effect in the Brent study is not clear. The inclusion and exclusion criteria were similar between the two studies, and the cognitive behavioural therapy method used in TADS was derived from the work of Brent and colleagues. Clarification of this discrepancy awaits further investigation.

Interpersonal therapy has been studied by two groups in both open and controlled trials for adolescent depression. Interpersonal therapy was, in one published randomised controlled trial, shown to be superior to a treatment-as-usual control and in another study both interpersonal and cognitive behavioural therapy were shown to be superior to a wait-list approach.

Given the large placebo, expectancy, or non-specific treatment contact effects on major depression through the lifespan, interpretation of studies comparing psychotherapy to treatment-as-usual or wait-list approaches must be regarded as providing less than definitive evidence for specific efficacy. Whereas the Brent study of cognitive behavioural therapy suggested an effect size of this therapy versus two other credible psychotherapies of similar size to that seen, for example, with fluoxetine versus placebo, the TADS study did not show a significant effect of cognitive behavioural therapy compared with pill placebo.

**Pharmacological treatment**

For adult major depression, tricyclic antidepressants, SSRIs, and specific norepinephrine reuptake inhibitors (SNRIs) all treat depression better than placebos and all are about equally efficacious, although it has been argued that mixed serotonin and norepinephrine reuptake blockers could have greater efficacy than SSRIs.

Although the separate studies are almost all quite small, considered separately or in aggregate there is simply no evidence of efficacy of tricyclic antidepressants for children and very little evidence of efficacy when considered overall in adolescents. The available aggregate sample size is insufficient to completely rule out meaningful antidepressant effects for tricyclic antidepressants, but is sufficient to suggest less efficacy than is seen in adults and possibly almost no efficacy at all in youth.

Table 1 provides the efficacy data for all randomised controlled trials of post-tricyclic antidepressants in youth that we could find. There is well-replicated evidence of efficacy for fluoxetine, reflected in the FDA approval of this compound in the treatment of depression in children and adolescents. Other compounds have at most a single positive study or solely negative studies.

In one industry-funded study paroxetine was shown to be superior to pill placebo on several measures of depression, but not on the predefined outcome measures. However, two subsequent industry-funded studies did not find any evidence of efficacy.

In response to FDA requirements of two positive studies to get an indication, Pfizer completed two studies of sertraline in children and adolescents, using identical methodology. Neither study, considered separately, reached statistical significance. But when all data from both studies were combined, sertraline was significantly better than placebo. Interpretation of these results has been contentious. On the one hand, this combined analysis was pre-planned at the time of study design and includes all studies done to date on the treatment of depression in youth. On the other hand, the difference in response rate between medication and placebo was small, about 10%.
In one of two studies, citalopram was significantly better than placebo and one of two studies of nefazodone has provided some evidence of the treatment’s efficacy. Available information on all studies to date of escitalopram, venlafaxine, and mirtazapine suggests that they have not shown superiority to placebo. However, the data from these studies are not yet published (table 1).

In those studies showing statistical superiority of the active compound, the overall response rate difference between active compound and placebo ranges from a high of 26% to a low of 10%. The placebo response rate across available positive studies ranges from 33% to 59%. Not surprisingly, the higher the placebo response rate across studies, the lower the difference between placebo and active compound.

Anxiety disorders, excluding obsessive compulsive disorder and major depression, seem to have shared genetic liability. By contrast with major depressive disorder, in which some studies are positive and others negative, SSRI treatment of both obsessive compulsive disorder and non-obscene compulsive anxiety disorders in youths seems robustly better than placebo treatment. This finding suggests that SSRI treatment of comorbid anxiety and major depressive disorder in youth might be a useful treatment strategy and certainly is deserving of controlled study.

Long-term treatment and prevention of relapse and recurrence
The rationale for continuation treatment is strong and rests on two foundations: 1) episodes of depression are bad during the episode itself, and, subsequently with suffering, increased risk of suicide, and impairment at home and school; 2) longer episodes of depression can increase the risk for future subsequent episodes—termed the kindling hypothesis. Short-term treatment does not seem to change long-term outcome after the discontinuation of treatment.

Most youth depression treatment studies have focused on acute treatment, although some have had a longitudinal follow-up component. The limited available data suggest that the pattern of remission, recovery, and relapse in recovery, and then recurrence over time while on medication could be like that seen in adults. Emslie showed significant superiority of a 32-week fluoxetine continuation after successful fluoxetine treatment over randomised discontinuation.

There are few data on the prevention of depression in youth. A study by Clarke and co-workers assessed adolescents who had current significant subsyndromal depressive symptoms and who had a parent who was being treated or had been treated for depression within the past year. In that study, group cognitive behavioural therapy was significantly better than usual care in preventing the onset of major depression during treatment and during a 14-month follow-up period, although the treatment-versus-control difference decreased with time.

Most youths with major depression get at least some services; however, most such services are unsystematic and brief, far below the level of treatment indicated by current efficacy studies.

Treatment side-effects
Excluding the issue of suicidality, the side-effect profile of SSRI and other newer antidepressants seems similar in youths to that seen in adults. Therefore, we will not discuss these other relatively common and generally readily managed side-effects. The overarching question is whether or not antidepressants increase the risk for suicide in depressed adolescents and, if so, whether and how these antidepressants should be used.

Suicide
There has been enormous attention to the possible risk of suicide with SSRI treatment for adolescent depression over the past 2 years. On July 10, 2003, after a reanalysis of data submitted by GlaxoSmithKline, the UK’s Medicines and Healthcare Products Regulatory Agency (MHRA) recommended that paroxetine not be used in treating children and adolescents younger than 18 years of age who have major depression. In August, 2003, Wyeth sent a letter to physicians stating that venlafaxine was not recommended for the treatment of depression in youths because of lack of efficacy and risk of increasing suicidal behaviour. In December, 2003, the MHRA stated that, with the exception of fluoxetine, SSRIs have not been found to be effective for depression in youths and can increase the risk of depression. The FDA met to review data addressing the same question in February, 2004, and met again after further analysis of all suicide data in September, 2004. In September, the FDA panel voted 18 to five to require manufacturers of all antidepressants (not just SSRIs) to add a black-box warning to their labelling. This label says, in part, “antidepressants increase the risk of suicidal thinking and behaviour (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders . . .”

On December 9, 2004, the European Medicines Agency (CHMP) issued a statement that it will inform clinicians, patients, and parents that while further investigations are being conducted that: “SSRIs/SNRIs are not authorised Europe-wide for the treatment of depression and anxiety disorders in children and adolescents. These compounds should generally not be used in this age group because clinical trials have shown an increased risk of suicidal behaviour (such as suicide attempts and suicidal thoughts). Nevertheless, a decision is sometimes taken, based on clinical need, to treat such patients. In these cases the patient should be carefully
In the study of Olfson, increased SSRI use between 1990 and 2000 within a geographic region was significantly correlated with decreased adolescent death by completed suicide within the same region, suggesting that either overall SSRIs are protective against suicide or that the conversion from tricyclic antidepressants to SSRIs decreased the rate of suicide. In a study of 49 completed adolescent suicides in Utah, none tested positive for SSRIs at the time of death. In another study of 66 completed suicides in children and adolescents in New York City from 1993 to 1998, in an analysis of a subgroup of 54 who had serum toxicological analysis for antidepressants at autopsy, only two had imipramine detected and two had fluoxetine detected.

Unfortunately, the current group of completed and ongoing studies of antidepressants in the treatment of children and adolescents were not designed to specifically address whether or not these compounds increase suicidality. Over a decade ago the question of SSRI increase of suicide in adults arose, but subsequent analyses showed that the available data did not lend support to such a link. Therefore the studies we have in children and adolescents have captured data related to suicidality in adverse-event reports, non-systematic elicitation of side-effects, and in various rating scales with one or a few suicide-related items done at intervals throughout the study.

The FDA meta-analysis found: 1) There were no statistically significant increases of suicide attempts, preparatory actions towards imminent suicidal behaviour, and/or suicidal ideation by compound for all randomised controlled studies for all disorders in children and adolescents (fixed-effect model) 85

<table>
<thead>
<tr>
<th>Agent</th>
<th>Risk ratio (95% CI)</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Fluoxetine</td>
<td>0·92 (0·79–1·08)</td>
<td>Does not include TADS data</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>2·65 (1·00–7·02)</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>4·97 (1·09–22·72)</td>
<td>Significant increase over placebo</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1·48 (0·42–5·14)</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>1·37 (0·53–3·50)</td>
<td></td>
</tr>
<tr>
<td>Remeron</td>
<td>1·58 (0·06–38·37)</td>
<td></td>
</tr>
<tr>
<td>All above agents together</td>
<td>1·78 (1·14–2·77)</td>
<td>Significant increase over placebo</td>
</tr>
</tbody>
</table>

Omnibus analysis repeated with random-effects model gave odds ratio of 1·59 (95% CI 1·03–2·46). All above agents together was well designed to address the issue of baseline measures of suicidality. Virtually none of the randomised trials was well designed to address the issue of suicidality. The difficulty with classification of the free-text data on the adverse-event forms as suicide-related or not is significant because many entries were ambiguous. Individuals were not randomised to achieve balance on baseline measures of suicidality or on other risk factors for suicidality. In summary, while the FDA analysis was methodologically very well done, the studies that it is based upon were not designed to examine suicidality and did not contain systematic data on suicidality. This issue restricts the interpretation of the results.

The FDA meta-analysis found: 1) There were no statistically significant increases of suicide attempts, preparatory actions towards imminent suicidal behaviour, and/or suicidal ideation by compound for all randomised controlled studies for all disorders in children and adolescents (fixed-effect model) 85
patients on placebo and 4% of patients on medication.
3) Examined covariates did not significantly predict suicidality during study in either group. 4) There was no evidence that suicidal events clustered at any particular time during the acute treatment (eg, they were not over-represented early in the treatment or at the time of medication discontinuation). 5) Examination by the FDA of the scores on suicide-related items on the various structured and semi-structured instruments used in these studies gave absolutely no indication of heightened suicidal ideation or attempts in patients on active medication versus placebo (risk ratio=0.92, 95% CI 0.76–1.11).

How then does one make a rational treatment decision given this signal of increased suicidality in the analysis of the adverse events reports, which persists despite thoughtful and comprehensive examination of study design issues and patient covariates? This signal contrasts strongly with data for a decrease in completed suicide that show strong correlation with the more widespread use of SSRIs within geographic regions and the overall decrease in completed suicide in youth and adults across countries. It also contrasts with the lack of signal of increased suicidality when looking at the structured rating instruments on the same subjects within these same studies.

One reasonable model is that some individuals could potentially have an increase in suicidality, which may or may not result in an increased risk for completed suicide. Other individuals might have a decreased risk for suicide with effective antidepressant treatment. The data above seem to lend support to both notions, although neither is yet definitively proven. The question then is not simply whether the net effect of using SSRIs to treat depression in youths in the population as a whole is protective, but rather the important clinical question is how to maximise the putative net protective effect by keeping to a minimum any potential component of increased risk. Such a model and approach is compatible with suggestions to increase monitoring of suicide-related ideation and behaviour in adolescents treated with antidepressants.

Conclusions
We have suggested elsewhere that future improvements in the treatment of depression in youth should concentrate on secondary prevention (eg, aggressive treatment of anxiety disorders to prevent progression to depression), improved and early ascertainment, more attention to successfully keeping children in treatment for the recommended course, and more systematic and consistent application of available research findings to all youths with depression.31

Cognitive behavioural therapy and interpersonal therapy are probably effective in the treatment of depression in youth. But clinicians trained to deliver these specific treatments are scarce or simply unavailable in many communities. Therefore, psychotherapy for depression in children and adolescents has a part to play but is not a panacea. There is good evidence for the efficacy of fluoxetine in child depression and some evidence for citalopram, paroxetine, and nefazodone, but little for other agents. Many of the negative antidepressant trials are available only as posters from scientific meetings or are not yet available. Regardless of the cause, this lack of availability has a significant adverse effect on rational clinical decision-making. Meta-analysis of all available trials would be extremely valuable to understand predictors of response and overall efficacy of broad classes of compounds. Most treatment studies examine acute treatment of non-refractory cases, leaving an enormous gap in our understanding of rational long-term treatment and treatment of refractory patients.

Completed suicide is not infrequent with adolescent depression. There have been no completed suicides of any subject in any youth antidepressant trial. There is a small but significant signal from the FDA meta-analysis of all suicide data related to randomised controlled trials of SSRIs and other new antidepressants for increased suicidality in the treatment groups compared with placebo groups. Adolescents who attempt suicide are a thousand fold more prevalent than those who complete it. Therefore, the link between increased suicidality in the FDA analysis and an increase in completed suicide in depressed youths taking antidepressants is a strong possibility, but not necessarily proven, and it is not possible to estimate the number of increased deaths that might be attributable to antidepressants used in the treatment of depression in youth. Epidemiological data showing a decrease in suicide with increased SSRI use and the very low rate of SSRI in the toxicological analysis of completed teenage suicide cases suggest that the net effect of antidepressant treatment might actually be a decrease in the hazard of youth suicide. Close monitoring of youths on antidepressant treatment, although not proven, could help decrease potential suicide risk.

The chronicity, morbidity, and mortality associated with depression in youths make the current state of knowledge a cause for great concern. The clinician faced with a depressed child or adolescent cannot in good faith merely suggest waiting for the healing effects of time.

Conflict of interest statement
N D Ryan has served as a consultant to Pfizer, Abbot, GSK, Wyeth Ayerst, BMS, Hoffman La Roche, AstraZeneca, Jansen, and Forest Laboratories on the design and interpretation of studies of child and adolescent affective disorders and related areas. He has been an investigator on two industry-funded studies, both of which are included in this article, a multi-site study of paroxetine in adolescents funded by GSK, and a multi-site study of venlafaxine in youth funded by Wyeth Ayerst.

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Seminar


61 Milin R. Presented at AACAP annual meeting. Chicago, USA, October, 1999.


