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RACE/ETHNICITY AS A MODERATOR IN CHILD AND ADOLESCENT DEPRESSION AND ANXIETY TRIALS

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ABSTRACT

The inclusion of racial/ethnic minorities in treatment outcomes trials for children and adolescents with depression and anxiety is essential, particularly given the assumption, required by the NIH, that racial diversity is important to the generalizability of clinical trial outcomes. A search for randomized clinical trials on the treatment of child and adolescent depression and anxiety was conducted using the *Medline* and *Psychinfo* databases. These were then reviewed to determine whether race or ethnicity were 1) factored into recruitment strategies; 2) represented in the trial sample; and 3) included in moderator analyses to determine the extent to which they may influence trial outcomes. 37 original and 13 follow-up trials were identified (total N = 3330). None identified strategies for targeted recruitment of racial/ethnic minorities. Six did not report race. All minority groups except for Native Americans are underrepresented as compared to 2000 US Census figures; however, only one study reported Native Americans as participants. Overall, 67% of the sample was Caucasian, 26% minority, and 6% unreported. There was no trend in minority representation by year. Most studies reviewed do report the ethnic breakdown of their sample population, although methods vary. Six studies, three original and three follow-up, explored the ethnicity as a moderator. Without an increased presence of minorities in clinical trials, it is unclear that the results of these studies can reliably generalize to a diverse population. The importance of studies in minority samples becomes apparent, as does the need for a greater emphasis on recruitment.

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TABLE OF CONTENTS

INTRODUCTION

Depression

Depression is, according to the World Health Organization (WHO), "the leading cause of disability as measured by YLDs[1] and the 4th leading contributor to the global burden of disease (DALYs[2]) in 2000." [1] Perhaps even more worrisome, studies seem to indicate that the presentation of depression during childhood or adolescence is common, often chronic, and associated with high levels of morbidity and mortality from suicide. [2] The National Comorbidity Study, while it did not focus exclusively on children and adolescents, found the highest 30-day prevalence in the youngest age group studied, 15-24 year olds. [2] In a 10-year review of depression, Birmaher et al. report that the estimated lifetime prevalence of depression in adolescents ranges from 15% to 20%. [3] It is also noted that the suicide rate for teenagers has increased rapidly in the latter part of the 20th century, quadrupling since 1950. This rapid rise also holds true for African-Americans, especially in more recent years. According to the Centers for Disease Control (CDC), African-American males aged 15-19 experienced a 146% increase in suicide rate between 1980 and 1995. [4] In a study of suicide in over 1,000 predominantly poor African-American adolescents, Iolongo et al. found the lifetime prevalence of suicidal ideation to be 5.3%. [5] A 2004 study reported that lifetime prevalence of major depressive disorder was 9.4% in a demographically similar population. [6]

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[1] Years lived with disability.
[2] Disability-Adjusted Life Years

Although the exact causes and/or mechanisms of depression are unclear, the possibility of a genetic component to the disease remains. Birmaher et al. report that children who grow up with at least one depressed parent are much more likely to experience an episode of major depression in their lifetime. [3]

Anxiety

Anxiety disorders, the most common mental health disorders, similarly affect populations worldwide. "Anxiety disorders not only are common in the United States, but they are ubiquitous across human cultures." [7] Among adults in the United States aged 18-54, the estimated 1-year prevalence is over 16%. [7] As with major depressive disorder, there is significant chronicity and morbidity associated with anxiety disorders. Some studies have found anxiety disorders, specifically panic disorder, to be linked to suicide attempts. [8] Again, as with depression, anxiety disorders appear to be common in children and adolescents. Various studies of anxiety disorders report that prevalence can range from 5.7% to 17.7%. In a 21-year longitudinal study of almost 1000 children from New Zealand, Woodward and Fergusson found the presence of an anxiety disorder in adolescence to be associated with a number of later negative outcomes. These include later mental health problems (including suicide), drug use, and "educational underachievement." [9]

Treatment Options

In the 1980's, the number of randomized controlled trials exploring possible treatment options for children and adolescents with depression and anxiety began to rise steeply.

However, a larger amount of clinical trials looking into the safety and efficacy of treatment options in depression and anxiety have been directed at adults. Despite this, pharmacologic as well as therapeutic treatment of young people with depression has been widespread. It is unclear whether results from adult populations can, or should, be extrapolated to include children and adolescents. In addition, the effectiveness of some of these treatment options, especially for young people, has yet to be established. One recent study [10], for example, found that although clinical trials have proven cognitive-behavioral therapy to be efficacious in the treatment of youth with depression, community clinic treatment of young people with depression has not proven to be as beneficial for patients, with results comparable to no treatment at all. These issues have become more controversial given the recent questions surrounding the safety and efficacy of SSRI use in children and the "black box" warning labels now required on such medications.

Treatment-Seeking

Many people, children and adults alike, do not seek treatment for mood disorders. As noted by the Surgeon General in the 1999 Report on Mental Health, "nearly two-thirds of all people with diagnosable mental disorders do not seek treatment." [11] Of those that do, many seek care from primary care practitioners rather than specialists in the field. One of the most significant reasons for this lack of treatment-seeking and utilization of specialists is the role of stigma in mental health care, which the Surgeon General's office reports may be linked with fear of the violence can be associated with mental health disorders. [11] However, there may be other issues at play. One study, for example,

found that while the utilization of mental health services in San Francisco's Chinatown was minimal, this was more likely to be due to a decreased level of acculturation, and lack of information about available services, than stigma. [12]

The role that demographic factors such as race or ethnicity may play in treatment-seeking behavior is somewhat unclear. In 1987, Sussman et al. [13] found the proportion of African-Americans fearing mental health treatment to be 2.5 times higher than White patients. When examining attitudes towards ADHD and its treatment, Bussing et al. found that African-American parents of children meeting ADHD criteria were less likely to use medical labels than White parents. [14] African-American parents also expected a shorter course of treatment. It has been reported that African-Americans are less likely than Caucasians to visit mental health professions. [15] While there are differences in insurance rates between Blacks and Whites, it has been found that the possession of above-average mental health coverage increases treatment-seeking among Caucasian patients more than in African-Americans. [16] In a study of the Epidemiologic Catchment Area Program, Gallo et al. also found that White Americans were significantly more likely to have consulted a mental health specialist in the 6 months prior to the interview than African-Americans, Hispanics, and other minority groups. [17] However, other recent research has stated that Latino patients, while less likely to approve of antidepressant medications, are also more likely to support counseling than Caucasians or African-Americans. [18] In a follow-up study to one initially conducted in 1981, Cooper-Patrick et al. reported that while at baseline African-Americans were initially less likely than Caucasians to receive mental health services, use among African-

Americans patients increased over the 1980's. [19] By follow-up in the mid 1990's, Black patients were as likely to utilize mental health services offered in general practitioner offices as White patients. While there has been much research on treatment-seeking behavior in mental health, it is clear that continuing study is called for, especially as pertains to children and adolescents.

Health Disparities

The IOM report on disparities, "Racial and Ethnic Disparities in Health Care," found that many health disparities exist, in a variety of medical specialties. African-Americans in the United States have higher mortality rates. This is especially striking in the case of African-American males as well as in infant mortality, which for Black patients is twice that of Caucasians in this country. A significant difference in infant mortality exists even when other socioeconomic factors, such as income, are controlled for. [15] It has been shown that African-Americans, in particular, suffer from higher rates of various diseases, with poorer outcomes. Black patients also suffer from higher morbidity rates in diabetes (three times that of White patients), heart disease (40% higher), HIV/AIDS (seven times higher), prostate cancer (twice as high), and even breast cancer, despite the fact that more African-American women undergo screening by mammography. [15]

The IOM report also looked into possible explanations for these various differences in health outcomes. The authors examined over 100 studies in the area of health disparities, and discovered that even when controlling for other demographic factors such as income, age, insurance status and education level, a majority of the studies found that racial and

ethnic minorities were less likely to "receive needed services, including clinically necessary procedures." [20]. The report hypothesizes that one possible reason that racial and ethnic minorities receive lower quality health care than White patients is due to a subconscious racial bias that physicians may possess. It also cites various studies that, for example, have shown that doctors, when presented with the same written description of a patient's case except for the race of the patient, have offered treatment recommendations that differed.

Of particular relevance to this review, it has also been found that ethnic minorities receive substandard mental health care. [11, 21] In addition, the increased amount of fear of mental health treatment amongst African-American adults mentioned earlier [13] is likely related to the fact that African-Americans have been found to have increased rates of involuntary hospitalization when compared to Caucasian patients with similar psychopathology levels. [22] Among young people in particular, African-American children have been found to be more likely to have "unmet need[3]" than Caucasian children. [15] Some studies have reported higher rates of certain mental health disorders such as obsessive-compulsive disorder and conduct disorder, along with depressive symptomology and enuresis, among minority children. Also of note is that 42% of children in foster care have been found to meet DSM-IV criteria for a mental health disorder. [23] Minority children are over-represented in the foster care/child welfare system.

[3] Those with documented impairment due to mental illness who have not received mental health care in preceding six months.

Attitudes toward medicine/research

Studies have been done relating race and/or ethnicity to attitudes towards the medical profession in general, with African-American adults being more likely to distrust doctors [24], including those running clinical trials. [25] Black patients are more likely to have heard of the Tuskegee syphilis experiment[4] than White patients. [25, 26] This lack of trust in the medical profession may contribute to researchers experiencing increased difficulty when attempting to recruiting minority patients into medical trials, in particular when there are no directed attempts at minority outreach. For adults with depression, race/ethnicity, in particular, has been found to be significantly correlated with treatment-seeking, the acceptability of certain kinds of treatments over others, and also the clinical setting in which depressed patients are most likely to seek help. Minority patients have been found to be more likely to visit primary care practitioners or emergency rooms than mental health professionals. [27] African-Americans have also been found to be significantly more likely to exclusively consult friends and/or family members about mental health issues, rather than doctors or other healthcare providers. [27] Attitudes towards the health profession in general, and mental health practitioners specifically, may affect patients' decisions about participating in clinical trials, seeking help, or even the effectiveness of therapy or other treatments.

NIH Revitalization Act of 1993

The number of randomized controlled clinical trials testing the efficacy and effectiveness of both pharmaceutical and therapeutic treatments is on the rise. However, the

[4] Observational study of syphilis outcomes in which African-American male patients with syphilis were not informed of their diagnosis, and continued to be followed, untreated, after the advent of penicillin treatment.

generalizability of these trials, based on demographic factors including race and/or ethnicity, is an important issue, one that the United States government as well as the National Institutes of Health (NIH) have acknowledged. This is especially true given the existence of a multitude of health disparities, and the lack of clear rationale for these inconsistencies in health and health care.

The NIH Revitalization Act, signed into law by President Clinton in 1993, directed the National Institutes of Health to create a set of guidelines for the inclusion of women and racial/ethnic minorities in clinical research. The purpose of the proposed guidelines was to supplement existing guidelines in four ways; by ensuring that 1) women and racial minorities were included in clinical research, 2) cost would not be permissible as a factor in excluding women and minorities, 3) the NIH would start and assist in outreach efforts for women and minorities in studies, and finally that 4) clinical trials would be

> …designed and carried out in a manner sufficient to provide for valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial. [28]

The statute also states that the exclusion of women and minorities is only to be allowed under certain circumstances, such as when either the health of the participants or the purpose of the research deems inclusion unacceptable, or if past research strongly refutes the possibility of a difference in outcome or severity due to gender or race.

NIH Guidelines of 1994, Amended 2000 & 2001

In 1994, the National Institutes of Health published a set of guidelines mandating the inclusion of women and minorities in clinical research, as directed by the NIH

Revitalization Act of 1993. Since that time, all clinical research funded by the NIH has been required to meet these minimum standards. In addition to representation of women and racial/ethnic minorities in clinical trials, the NIH Guidelines also require each research proposal to include a description of outreach programs to recruit these underrepresented groups. However, the "valid analysis" required by the Revitalization Act is defined by the NIH as "an unbiased assessment," [28] including randomization into groups and use of unbiased outcomes evaluation and statistical analysis among groups. The Guidelines do not require every NIH - funded clinical trial to have the statistical power necessary to explore possible differences due to gender or race/ethnicity. They also report that analyses should look for a "significant difference," of public health or clinical importance, rather than a "statistically significant difference." [28]

The two later amendments to the NIH Guidelines, in 2000 and 2001 [29], were primarily created to redefine the term "clinical trial" as well as the process of data collection on race and ethnicity. Specifically, the NIH now mandates the use of racial and ethnic categories as defined by the United States Office of Management and Budget. Researchers are required to first ask participants to classify their ethnicity into one of two categories: 1) Hispanic or Latino and 2) Not Hispanic or Latino. Participants should then have the option of categorizing their race into one or more groups. These include: American Indian/Alaska Native, Asian, Black/African-American, Native Hawaiian/Other Pacific Islander, or Caucasian. This is the same process used during for the 2000 US Census.

Race & Ethnicity: Definitions & Stress

It has been maintained that the NIH Guidelines described above were created in an attempt to ensure that the science behind clinical trials is generalizeable to a larger population, rather than due to political reasons or popular opinion. [30] It can be argued that the use of race and ethnicity in clinical trials is important because double-blind studies, in particular, may offer one of the few ways to display any potential ethnic and/or cultural differences in mental illness and treatment without bias, or at least with significantly decreased bias. However, along with a mandate to produce studies containing larger numbers of minority subjects comes the question of the definition of both race and ethnicity, as well as how to best approach analyses involving these variables. In a 1996 special supplement, the Journal of Consulting & Clinical Psychology published a number of articles regarding the implementation of the NIH Guidelines, including two that addressed the concepts behind demographic factors such as race and ethnicity. [31, 32] Beutler et al., in a review of articles published in three journals between 1970 and 1993, reported that demographic variables such as race, ethnicity, sex, gender, and age, were "not used consistently and lack empirical and conceptual validity." [31] They argue that these should be considered as constructs rather than immutable characteristics, and as such, investigators should report the definitions and explain the use of each term in clinical research. In addition, they specify that the word 'ethnicity' should be used in lieu of 'race' whenever the implication of a cultural vs. biological basis for the construct exists.

The potential for misuse is often cited as reason to be wary of considering race or ethnicity in clinical trials. Science has a history of being used as justification for the mistreatment and continued oppression of people of color. [33, 34] One potential reason for the lack of minority representation in clinical studies and the lack of analysis of potential effects of race or ethnicity is that investigators may lack experience with multi-cultural or underrepresented populations. As such, many may be wary of attempting to interpret differences attributed to ethnicity, or believe that multiple different hypotheses are required in order to address each racial or ethnic category. [32] When investigating potential differences in outcomes based on ethnicity, however, an important consideration is the role that minority status[5] may play in results. Past research has found that among ethnic minorities in the United States, life experiences are shaped by minority status. [35] in [32] Because of this, it may be important for clinical research investigators to include a set of questions, or tools, to assess such issues including the amount stress encountered by participants. The importance of this is highlighted by the fact that 60% to 70% of adults who suffer from depression have been found to have undergone one or more losses, or other life events rated as severely stressful, in the one year preceding onset of the depressive episode. [3]

Moderators/Secondary Analyses

A moderator is defined as a variable that precedes treatment and is unchanging, at least during the course of treatment. It has the potential to affect treatment outcomes, but is uncorrelated to treatment. [36] Moderators are essential when attempting to assess the

[5] Defined by Alvidrez et al. as: "the designation of members of particular groups as inappropriate, unwelcome, or inferior, that justifies and perpetuates their systematic exclusion from full participation in society or access to its rewards"

effectiveness of a particular treatment option, for example, as they can help identify specific populations or sub-populations that may experience different treatment outcomes. They "specify for whom and under what conditions an intervention works." [36] Mediators, on the other hand, may change during treatment (such as treatment adherence or dosage), and have been shown to have a role in determining the mechanism of action of treatments. [36, 37] The terms mediator and moderator are mutually exclusive. The classification of a variable as a moderator or mediator is done through secondary analyses, which increases the risk of type II errors while remaining at risk for type I errors. [37] Researchers can determine which variables to explore as potential moderators or mediators based on previous data or theory; these analyses are considered to be methods of creating new hypotheses rather than testing them. [36] In addition, as opposed to other types of research, the effect size is prioritized over the P value. A moderate or large effect size points to the possibility of clinical differences that were unable to reach significance due to limited power. Predictors are related to treatment results, but in a non-specific way: they are not linked to treatment assignment, and are uncontrolled. [37]

STATEMENT OF PURPOSE/HYPOTHESIS

Beginning with the assumption (required by the NIH) that racial diversity is important to the generalizability of clinical trial outcomes, I hypothesize that all pediatric depression and anxiety clinical trials will (1) include specific minority outreach plans as part of recruitment; (2) include data on minority participation in the sample description; and (3),

include a moderator analysis specifically devoted to race/ethnicity. As a comparison, race will be compared to gender and SES, two other important demographic variables.

There is more work to be done in the field of treatment for child & adolescent mood disorders. It has been found that some pharmacological and therapy-based treatments can be efficacious when treating youth, but it becomes important to design such treatments to be as effective as possible. While generalizations and stereotypes can be dangerous, differing beliefs about treatment may require physicians to better design outreach and treatment methods to suit the particular population(s) with which they are working (which may or may not differ based on demographic variables such as age, socioeconomic status, and race). The aim of this literature review is to consider the trials that have already been done in this area (reviewing the use of these demographic factors), and define research areas of need in this field. The broad goal is to ensure that prevention strategies and treatments for depression are able to be as valuable as possible.

METHODS

Literature Review

Published randomized controlled trials on the treatment of child and adolescent depressive and anxiety disorders from 1994 through December 2005 were identified using the *Medline* and *PsychINFO* databases. Search terms included *depression*, *dysthmia*, *bipolar*, *anxiety*, *separation anxiety*, *selective mutism*, *panic disorder*, *phobia*, *child*, and *adolescent*. Psychosocial and psychopharmacological treatment studies that employed a control or a comparison condition were evaluable. Medline searches were

limited to the English language, with *Randomized Controlled Trial* as the publication type, and to *All Infant* (birth to 23 months), *Pre-School Child* (2-5 years), *Child* (6-12 years), or *Adolescent* (13-18 years) for age. Because of the inclusion of age 18 under the *Adolescent* group in Medline, many adult studies were recovered. These were excluded. PsychINFO searches were also limited to the English language, with Clinical Trial as the Form/Content Type, and Childhood (birth-12 years) or Adolescence (13-17 years). Systematic reviews in peer-reviewed journals and the reference lists of identified trials were used to retrieve additional articles. Studies conducted entirely or in part (i.e. one site of a multi-site study) outside of the United States of America[6] were excluded due to the use of US Census data as a comparison for racial representation. Those dealing with Obsessive-Compulsive Disorder, Post-Traumatic Stress Disorder, Tourrette's Syndrome, and Trichotillomania were also excluded. Follow-up studies of randomized controlled trials were included when they themselves were classified as RCT's. However, to ensure that no information was replicated, these follow-up studies were not factored into reviews of recruitment strategies nor into the analysis of representation unless such information was excluded from the original trial. In this case, the information from the first follow-up study to report recruitment/demographic data was utilized.

The 37 original trials and 13 follow-up studies identified (See Tables 1 and 2) were then reviewed for the extent to which race/ethnicity and other demographic factors were 1) factored into recruitment strategies; 2) represented in the trial samples; and 3) included in moderator analyses to determine the extent to which they may influence trial outcomes. When possible, the treatment of race, gender, and socioeconomic status as demographic

[6] This includes the 50 states and the District of Columbia, but not Puerto Rico

variables and potential moderators were compared. When looking at overall trends, we have combined each individual minority grouping into one category, given the small number of participants in each group.

Census Data

US Census Data was obtained from the US Census website <factfinder.census.gov>. Inter-census population estimates were also obtained from this website. Both the 1990 and 2000 US Census (as well as population estimates) distinguish between race and ethnicity; all participants were asked to report their race as well as whether or not they considered themselves to be of Hispanic origin (Spanish, Hispanic, or Latino). In the 1990 Census, respondents were asked to identify their race within one of five categories: "White," "Black or African American," "American Indian and Alaska Native," "Asian," and "Native Hawaiian and Other Pacific Islander." Of note, the 2000 Census included a sixth grouping, "Some other race," and also allowed each participant to select more than one of these six categories when describing own race. Despite this, 98% of people reported only one race. 97% of respondents who only reported themselves as "Some other race," are of Hispanic origin. [38]

When reporting Census information from 2000 or afterwards, we use "one race alone" responses as an estimate for racial representation in the United States, with the understanding that while this does not take into account ~2% of respondents, it better allows for comparison across the years given that earlier respondents were not given the option of choosing more than one racial category. Specifically, since NIH guidelines

include the use of Hispanic/Latino as a “minority group”, we use the “one race, not Hispanic” data for the racial categories described above, and use “Hispanic, any race” data to estimate the number of Hispanics/Latinos in the United States.

RESULTS

Recruitment Methods

One study [39], 2.7% of the total number of original trials, did not describe recruitment methods used.

The majority of studies (78.4%) [40-68] reported that patients were recruited through school referrals, media advertisements, referrals from health care providers, or a combination of these three. Seven (18.9%) [69-75], however, differed in their approach. Two [69, 72] recruited patients from consecutive inpatient admissions for depression and bipolar disorder. These were the only trials in which participants were not recruited as outpatients. In fact, many of the reviewed studies included recent or current inpatient admission as part of their exclusion criteria.

The remaining five trials [70, 71, 73-75] instead screened out eligible participants from larger previously defined populations (such as students in particular schools or HMO members) that were not self-referred or referred by others. Four of these trials [34, 70, 73, 75] began with one or more schools, offering screening tests to discover potential subjects and then randomizing identified students into treatment groups. Thompson et al investigated suicide prevention methods by initially identifying students deemed at-risk

for dropping out of school from seven urban high schools in two school districts in the Pacific Northwest, based on various criteria such as attendance and academic performance. They then offered screening specific for suicide risk. While all four high schools in one district were included, only three in the second district were selected. This decision was based on "their geographic and demographic representation of that district's 10 high schools." Clarke et al. [70], Lamb et al. [73], and Weisz et al. [75] used a similar strategy, identifying students with depression or "depressive symptomology" [73] from a rural high school [73], 3 suburban high schools[70], and three elementary schools [75]. While the choice of high schools in Thompson et al was at partially explained, none of the three other studies offered a comparison of their schools' racial composition to that of the geographic area in which they are located.

Clarke et al. [71], on the other hand, searched for depressed parents and children from an initial sample of about 410,000 patient records from a Health Maintenance Organization previously shown to be somewhat representative of the local population. They ended with 88 participants.

Two studies, recruiting from outpatient clinics, specifically stated that they did so "without regard to race, gender, or ethnicity." [48, 68] In a follow-up article to the TADS study, however, it is reported that part of the selection process for sites was based on the "demographic composition" at the clinics. [76] None of the trials reviewed revealed explicit attempts at recruiting women or minorities into the studies, although in both studies by Mufson et al. [55, 67] the population was exclusively comprised of adolescents

referred to school-based health clinics in New York City, meaning that participants were limited to students at those particular schools. The studies referred to the fact that the schools were located in "urban, impoverished areas." [67]

Representation

Six of the thirty-seven original studies (16.2%) did not report race or ethnicity in any way (See Table 3). Of these, only one [59] had at least one follow-up RCT published [77] in which the racial composition of participants was reported. Of the thirteen follow-up studies themselves, five [78-82] did not report the representation of different racial categories in the study population. However, all of these did have race reported in either the original study or another follow-up series. The remaining eight reported race in some way. [37, 76, 77, 83-87]

Ten of the initial studies (27.0%) failed to describe the specific race/ethnicity of participants, instead forming two groupings: one comprised of Caucasians and the other of 'minorities' or 'other.' While two of these [45, 46] had subsequent follow-ups published, none of the seven follow-up trials included more detailed information.

Four studies [55, 56, 67, 74], or 10.8% of the total, reported equal or greater numbers of minority participants as compared to Caucasians. Two studies [41, 85], 5.4%, reported that 100% of the participants were Caucasian.

Overall, 3330 children and adolescents participated in these thirty-seven original clinical trials. Of these, 3082, or 92.6% of the participants, took part in studies reporting race and/or ethnicity. The majority of these young people described themselves as Caucasian (n=2213, 66.5% of the total, 71.8% of those studies reporting race). 288 (8.6% of total, 9.3% of reporters), were African-American; 277 (8.3% total, 9.0% reporters) were Latino; 89 (2.7% of total, 2.9% of reporters) were Asian/Pacific Islander, 18 (0.5% of total, 0.6% of responders) were Native American, and 6 (0.2% of total & reporters) classified themselves as "Mixed-Race". In addition, 190 (5.7% total, 6.2% reporters) were either grouped into an "other" category in those studies specifying specific races/ethnicities, or were categorized as "minorities" in those studies choosing not to specify race other than Caucasian. 248 of the 3330 total participants (7.4%) contributed to those studies not reporting race/ethnicity in any way in the original publication. Of these, however, 63 were participants in the Bernstein et al. [59] trial, for which a follow-up study detailing demographic data was published. [77] Therefore, the race and/or ethnicity was not reported for 185 children and adolescents (5.6%) contributing to published work. (see Table 3 and Figure 1)

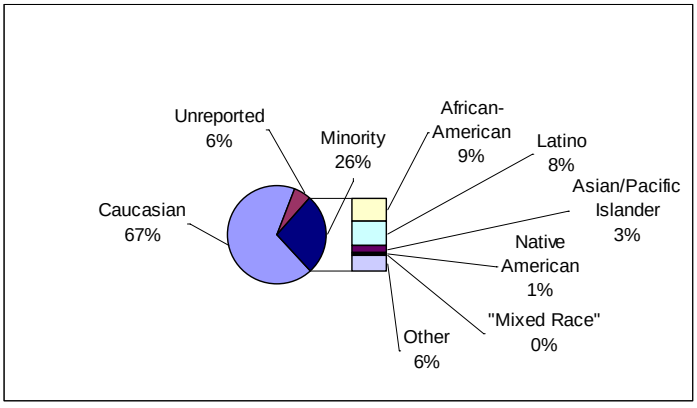

Figure 1. Minority Representation in Original Trials Reviewed

The large (n > 100) studies, of which there were nine, accounted for over half (59.8%) of the total participants. A greater percentage of these participants (70.9%) classified themselves as Caucasian, African-Americans (12.1%), Asian (4.2%), and Native American (0.9%). However, a lower percentage of subjects in the large studies consider themselves to be Latino (6.1%) and Mixed-Race (0%). As compared to all original studies, about the same proportion (5.8%) of participants were classified as minorities, or considered themselves "Other."

There were a larger number of studies conducted in the area of depression/bipolar (n=22) than anxiety/phobic disorders (n=15). In addition, there were far more participants (n=2336 vs. 994). 28.2% of participants in depression studies, and 21.1% of anxiety trial subjects, classified themselves as minorities. 11.2% of the subjects' race went unreported in anxiety trials, vs. 5.9% in depression trials. In studies of psychotherapy interventions only (21 studies with 2323 total participants), 29.3% of the children and adolescents were minorities. Race was unreported for 5.6% of them. In trials that included at least one branch testing pharmacotherapeutic options (16 studies, n=1007), race was unreported for 14.3% of subjects. 18.8% were minorities.

According to the 2000 US Census data, 69.4% of the US population defines themselves as White or Caucasian (not Hispanic), 11.8% as Black or African-American, 12.5% as Hispanic or Latino, and 3.7% as Asian, 0.6% as American Indian or Alaska Native, and 0.1% as Native Hawaiian or Pacific Islander. However, the yearly population estimates

from 1994 through 2005 show a fairly steady, if small, upward trend in terms of the percentage of people classifying themselves as racial/ethnic minorities. (Figure 3)

There are three years, 1996, 1999, and 2001, in which the percentage of minorities participating in reviewed clinical trials was greater than the percentage classifying themselves as minorities in US Census estimations. In 1996, only two original trials were reviewed, the larger of which (n=151) had a relatively large proportion of minorities, about one third. The smaller study (n=31) consisted of about one quarter. In 1999, the results were significantly affected by the fact that two of the four studies reviewed from that year had greater numbers of minority participants than Caucasian participants. Interestingly, one study of the four did not report race at all, and the remaining study from 1999 was almost 40% minority. Similarly, in 2001, study with the largest sample size reviewed, n=460, had a greater proportion of minority subjects than Caucasian subjects.

Although both the number of randomized, double-blind trials in the field of child and adolescent psychiatry as well as minority participation in these trials have generally increased since 1994, there does not seem to be an obvious trend in minority representation when studies are examined by year. This remains true when confidence intervals are taken into account. (see Figure 2) Of the eleven years examined in this review, only in four years did the proportion of minority participants approach or exceed the proportion of minorities living in the United States.

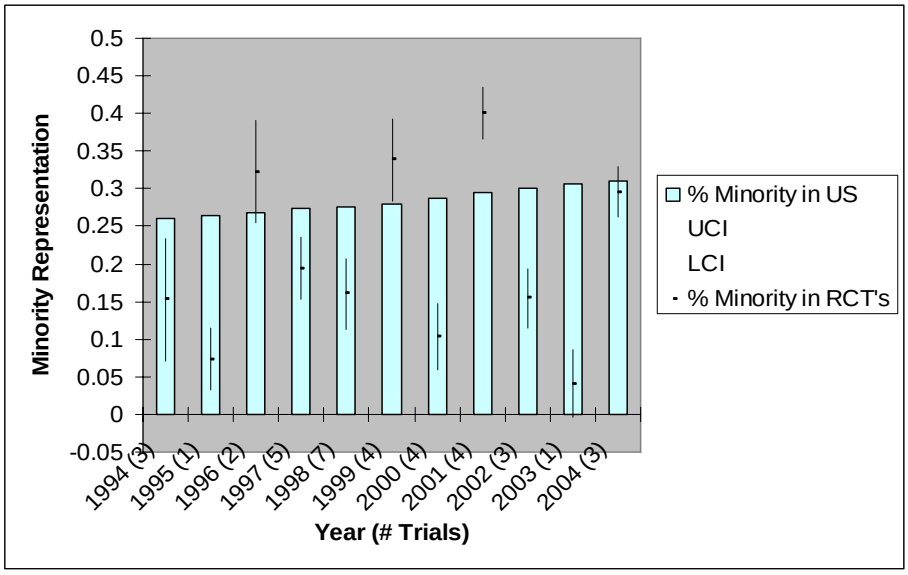

Figure 2. Minority Representation by Year (as Compared to US Census Data). UCI: Upper Confidence Interval. LCI: Lower Confidence Interval

Moderator Analyses

Of the original studies reviewed, nine made no mention of whether there were pre-treatment or randomization differences based on demographic variables. [41, 43, 45, 51, 53, 54, 61, 71, 75] Five, while discussing other demographic variables such as sex and age, did not include race/ethnicity. [40, 46, 50, 70, 73] Twelve used general phrases such as 'no differences between treatment groups based on demographic variables" without explicitly mentioning race. Of these studies, two did not report the race of the participants. [48, 59] Eleven discussed race or ethnicity, primarily in order to ensure the lack of pretreatment differences across groups, and/or between completers and non-completers. Of these, Treadwell and Kendall reported an increased number of African-Americans in the control group, and randomized to the wait list. Birmaher et al. commented that there were no African-American males in the study population. [69] Of note, every original study reviewed reported patient sex or gender along with age. One

study was noted to be entirely comprised of females; race was unreported in the trial. [61] Fifteen reported some form of socioeconomic status (SES) or income.

Eleven original studies did not otherwise mention race or ethnicity in the “Results” or “Discussion” (or equivalent) sections at all. Eight pointed out that more ethnically diverse samples were necessary, or cited “ungeneralizability” as a study weakness. Interestingly, the authors of one of these trials discussed that the study might not be applicable to the larger population due to the large numbers of Latino females in the sample. [55] Five either explored the possibility of race or ethnicity having an interaction or moderating effect, and/or discussed race or ethnicity as it pertained to treatment outcomes. [42, 44, 47, 56, 75] Of these, three (8.1%) explicitly explored the possibility of ethnicity as a moderator through analysis of variance (ANOVA) testing; it was found to have no moderating role in any. The other two point out that “comparable effectiveness” [47]is suggested across demographic lines.

Of the thirteen follow-up studies, six considered ethnicity when attempting to determine whether there were randomization or completer/non-completer differences. Three (23.1%) were written to look for possible moderators and mediators in depression [81, 85] and anxiety [37]. In all three analyses, no demographic moderators were found. In the RUPP article, however, race/ethnicity was initially found to have an effect size of 0.47 (with 0.5 being considered a moderate effect size). Further investigation showed that neither 3-way ($p=0.07$) nor 2-way ($p=0.33$) interactions were statistically significant. In addition, the TADS follow-up study looked at demographic characteristics, comparing

their population to previous work. The authors specifically mentioned the possibility of performing moderator and mediator analyses in the future, due to their large and diverse study population.

DISCUSSION

Recruitment Methods

Few trials demonstrate any directed attempts during recruitment to ensure racial/ethnic diversity. In those trials that screened out participants from a larger population, the choice of school, hospital, or HMO location proved to affect the diversity of the study sample population. For instance, in the two Mufson et al studies [55, 67], school clinics located within public schools in New York City were used as the site of the research, resulting in a high percentage of minorities, particularly Latinos. In the Thompson et al. study, the location of the seven urban high schools examined, in the Pacific Northwest, allowed for a greater number of minorities, particularly Asian/Pacific Islander and Native American. The study noted that the contributing schools had minority representations ranging from 34% to 60%. On the other hand, the Clarke et al. [71] trial noted that it screened the entire population of an HMO, also located in the northwest, that was representative of the surrounding area. Despite this, the final result was a sample 90% of which was Caucasian. It was not noted whether or not the HMO was located in an urban or rural area. Both studies that recruited directly from inpatient hospitalization ended with similar numbers of minority representation; Birmaher et al 1998 had a minority representation of 11.1%, while DelBello et al. was comprised of 16.7% minority participants. Both fell below the average for all studies reviewed. Of note, one multi-site

trial [68] documented, in a follow-up study also reviewed, that demographic make-up of potential sites played a role in their selection.

It is important to investigate the trials that ended with a greater number of minority participants, as well as those that ended with none, to assess whether recruitment methodology may have played a part in representation outcomes. Again, four studies had equal or greater numbers of minorities. Of these, only Silverman et al. 1999 utilized the most common form of recruitment, referrals from a variety of sources including schools and health professionals. The remaining three [55, 67, 74] recruited from school-based clinics based in urban public schools, greatly affecting the potential trial population from the start. Given the likelihood of any public school to approach or exceed minority representation on a local level, one feasible option for investigators seeking to augment the proportion of minorities in their trial seems to be to increase involvement . However, there are drawbacks as well, such as the possible restrictions placed on research by school districts.

The only trial reviewed with 0% minority representation was Graae et al. 1994, a study that reported the use of clinic and school sources along with newspaper ads as recruitment methods. Of the ten reviewed trials that utilized advertisements in any way, four did not report race/ethnicity. Overall, 196 of the 1036 total participants (18.9%) in these studies classified themselves as minorities. Of the three trials that reported only using methods of advertisements[7] as recruitment tools, none reported the race of their

[7] Local ads and/or announcements sent to schools/clinics

subjects. Three studies used advertisements as part of a large variety[8] of recruitment methods; in these, 27.0% of the participants were minorities. Given the differences in attitudes toward medicine and medical research experienced by persons of different ethnic backgrounds, it is possible that ad placement, while potentially reaching a great number of people, may be too impersonal a method to sufficiently reach a minority population. Interestingly, one study [45] reported that participants recruited via clinic referral were less likely to respond to psychotherapy than those recruited by advertisement. This was attributed to differences in hopelessness scores. The trial did not indicate whether method of recruitment was associated with race or ethnicity in any way.

As mentioned above, there are numerous examples of the ways in which race can play a role in the amount of trust a prospective study participant has in medical researchers and/or medical trials, and a number of historical reasons for this disparity. Such a lack of trust may make it significantly more difficult for investigators to obtain ethnically diverse samples, which is vital when attempting to tease out the possible role that race may play in treatment outcomes. However, this difficulty cannot be an excuse, especially given the emphasis in the NIH Guidelines on minority outreach methodology. Targeted recruiting methods exist; it is the role of researchers to ensure that their samples are representative. Training and increased education on this subject are essential. The NIH has published an "Outreach Notebook" as a tool to assist researchers with recruitment of minority participants. [88] In addition, there have been other series, such as the Journal of Consulting and Clinical Psychology's (JCCP) post-NIH Guideline supplemental issue in

[8] Four or more different methods used, including advertisements

1996. The articles included addressed a variety of issues surrounding the guidelines and their implementation, including the importance of recruitment methods.

In one article, the outreach methods utilized in a sizeable study of psychiatric inpatients in a low-income, urban area are described. [34] The authors describe a four-pronged approach to the recruitment of African-Americans with schizophrenia or mood disorders. Through a combination of a community partnership with a local mental health clinic, emphasis on interviewer selection and interviewer training, and an exploration of the role of cultural sensitivity through an assessment of ethnic matching[9], they were able to recruit a sizeable population of African-American patients. Of note, they found that ethnic matching did not affect refusal or completion rates; patients were more likely to refuse or drop out based on type of mental illness. [34] This is positive news for investigators interested in recruiting greater numbers of minority participants, particularly since it seems possible that the focus on interviewer training may have helped to overcome potential barriers based on race or ethnicity. However, it may also be valuable to recruit an increased number of minority researchers, given the fact that both the IOM and Surgeon General's Report state that minority medical professionals are more likely to work in areas comprised of minorities, and that in general, patient trust may be increased with doctors or researchers of the same racial/ethnic background.

Representation

Despite the fact that the majority do report in some way the racial/ethnic breakdown of their sample population, approaches to this process, as well as the level of specificity,

[9] Matching recruiter/interviewer and patient by race, ethnicity, cultural background, or a combination

varies from study to study. The majority of patients participating in these studies are classified as Caucasian. Overall percentages of African-Americans, Latinos/Hispanics, and Asian/Pacific Islanders participating in trial samples are lower than those reported in the US population as of the 2000 Census. While the proportion of Native Americans participating in these studies is equal to the proportion in the United States, only one reviewed trial (Thompson et al.) included any Native American participants. Looking at yearly US population estimates by race and ethnicity since 1994, there has been a small but steady increase in the percentage of the US population that is comprised of people self-identifying as minorities. In 1994, 26.0% of the US population classified themselves as minorities, while in 2004 that number was 31.1%.

This rise is primarily due to the proportion of Hispanics and Latinos in the country, which increased from 10% in 1994 to 14.2% in 2004. Given this fact, it becomes even more important consider the role of culture and language in treatment outcomes research. Many reviewed studies included language other than English as an exclusion factor, which may have decreased the number of minority patients able to participate, particularly in the Latino and/or Asian categories. The Spanish language is spoken by approximately 30 million US citizens over the age of 5. [89] The United States hosts the 5th largest Spanish-speaking community in the world. [89] One recent study not included in this review,[10] by Rossello and Bernal, did begin to address some of these issues. [90] With a study population that was 100% Hispanic/Latino, and Spanish-language interventions available, the trial referenced their use of culturally sensitive therapy. One reviewed study [67] allowed primarily Spanish-speaking students to participate in two

[10] Due to its location in Puerto Rico

sites (out of five); two others mentioned and briefly described their use of culturally sensitive therapy. [56, 57] Of note, these two trials had study populations comprised of 44.5% minorities, much higher than that of the US population. While shown to be effective in a number of trials, cognitive behavioral therapy (CBT) has also been shown to less efficacious in community samples than in trials. (Weersing and Weisz 2002) The inclusion of greater numbers of minority participants in studies, along with the increased use of 'culturally sensitive' therapy, may serve to better allow the transfer of CBT and other therapies in particular from the controlled trial to the clinic.

Moderator Analyses

Three of the original studies reviewed, 8.1%, specifically included ethnicity as a potential moderator as part of their analyses. In addition, there were three follow-up studies (23%) designed to search out the role of various demographic and other variables as moderators and mediators. Among the other studies that explored possible effects of race or ethnicity on treatment outcome, many discussed trends rather than reporting means. One follow-up study, citing their large and diverse sample size, did discuss future moderator and mediator analysis. [76] However, the majority of studies reviewed do not have the sample sizes or minority representation required to accurately assess the possibility of race or ethnicity as a moderator.

Limitations

Due to the variety of disorders and treatment options reviewed, a meta-analysis was unable to be done. Instead, a literature review, a less statistically rigorous method, was

performed on these trials. Because of this, it is impossible to estimate the role that race/ethnicity may play in child and adolescent depression and anxiety based on current outcomes research. Rather, this review serves to look at the research being done in this area, with an emphasis on the way that race and ethnicity are incorporated into outreach strategies, reporting methods, and analysis.

The methods used to identify trials, including Medline and PsychInfo searches as well as reviewing reference lists, may not have been all-inclusive. Some trials may have been missed. In addition, some of the exclusion criteria used in this review, particularly the limitation to those studies performed entirely within the United States, served to eliminate some important large and/or multi-site studies, such as the Rosselló and Bernal trial mentioned above as well as a 2004 multi-center trial investigating the use of paroxetine in Social Anxiety Disorder (Wagner et al.), to name only a few. Another important exclusion criterion was disorders such as OCD and PTSD, which may have overlooked trials that did include considerable numbers of minority participants and/or performed moderator analyses using race and ethnicity.

Future Research Needs

Based on this review, it seems clear that additional work needs to be done in order to correctly assess the existence of a relationship between race/ethnicity and treatment outcomes in child and adolescent trials in depression and anxiety. Given the differences between study populations and the US population with regard to race and ethnicity, the generalizability of many of the trials reviewed is uncertain. It is also unclear that

outreach methods currently being used are sufficient to recruit large numbers of minority participants. It is possible that more training is necessary for investigators in order to achieve adequate sample sizes as well as report accurately using NIH guidelines. Once this is achieved, it will become possible for a greater number of studies to investigate the possible role that race and/or ethnicity may play in the pediatric depression and anxiety trials.

Conclusions

There has been significant improvement in the inclusion of minorities in randomized controlled trials in the field of child and adolescent depression. However, minority representation in trials reviewed between 1994 and 2005 (inclusive) still lags behind US Census Data, both in average and also when compared on a yearly basis. There is no apparent trend when minority trials are aggregated by year; that is, as opposed to US Census data over the past 11 years, there has been no steady increase or decrease of minority representation in these clinical trials. Rather, it seems that some trials, particularly the larger multi-site studies along with those that are comprised of over 50% minority participants, have sizeable effects on the percentage of minority participants in a given year. Inclusion of minorities in clinical trials may be positively influenced by a shift in the focus of recruitment methods. The more universal consideration of demographic makeup during clinical site selection may prove to increase the number of minority participants in RCT's. Also, additional investigator training and/or sharing of "best practices" may encourage the use of targeted recruitment methods. As the proportion of minority subjects in child and adolescent depression and anxiety trials

increases, it will become possible for moderator analyses to be performed, so as to determine whether race or ethnicity have an affect on treatment outcomes or effectiveness of treatment options.

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Table 1. Original RCT's Reviewed (1994-2005)

Year	Author(s)	Title	Disorder	Treatment
1994	Black and Uhde	Treatment of Elective Mutism with Fluoxetine: a Double-Blind, Placebo-Controlled Study	Selective Mutism	Fluoxetine
1994	Graae et al	Clonazepam in Childhood Anxiety Disorders	Anxiety	Clonazepam
1994	Kendall et al.	Treating Anxiety Disorders in Children: Results of a Randomized Clinical Trial	Anxiety	CBT
1995	Clarke et al.	Targeted Prevention of Unipolar Depressive Disorder in an At-Risk Sample of High School Adolescents: A Randomized Trial of a Group Cognitive Intervention	Depression	GCBT
1996	Kye et al	A Randomized, Controlled Trial of Amitriptyline in the Acute Treatment of Adolescent major Depression	Depression	Amitriptyline
1996	Treadwell and Kendall	Self-Talk in Youth With Anxiety Disorders: States of Mind, Content Specificity, and Treatment Outcome	Anxiety	CBT
1997	Brent et al	A Clinical Psychotherapy Trial for Adolescent Depression Comparing Cognitive, Family, and Supportive Therapy	Major Depression	CBT, SBFT, NST
1997	Emslie et al	A Double-Blind, Randomized, Placebo-Controlled Trial of Fluoxetine in Children and Adolescents with Depression	Depression	Fluoxetine
1997	Kendall et al	Therapy for Youths with Anxiety Disorders: A Second Randomized Clinical Trial	Anxiety	CBT
1997	Sallee et al	Pulse Intravenous Clomipramine for Depressed Adolescents: Double-Blind, Controlled Trial	Depression	Clomipramine
1997	Weisz et al	Brief Treatment of Mild-to-Moderate Child Depression Using Primary and Secondary Control Enhancement Training	Depression	Prim & Sec Control Enhancement Training
1998	Ackerson et al	Cognitive Bibliotherapy for Mild and Moderate Adolescent Depressive Symptomatology	Depression	Cognitive Bibliotherapy
1998	Birmaher et al	Randomized, Controlled Trial of Amitriptyline Versus Placebo for Adolescents with "Treatment-Resistant" Major Depression	Major Depression	Amitriptyline

1998	Geller et al	Double-Blind and Placebo-Controlled Study of Lithium for Adolescent Bipolar Disorders with Secondary Substance Dependency	Bipolar	Lithium
1998	Geller et al	Lithium for Prepubertal Depressed Children with Family History Predictors of Future Bipolarity: A Double-Blind, Placebo-Controlled Study	Depression	Lithium
1998	Klein et al	Adolescent Depression: Controlled Desipramine Treatment and Atypical Features	Depression	Desipramine
1998	Lamb et al	School-Based Intervention to Promote Coping in Rural Teens	Depression	School-based CBT
1998	Last et al	Cognitive-Behavioral Treatment of School Phobia	School Refusal	CBT
1999	Clarke et al	Cognitive-Behavioral Treatment of Adolescent Depression: Efficacy of Acute Group Treatment and Booster Sessions	Depression	GCBT, GCBT + parent group; + "Booster" sessions
1999	Mufson et al	Efficacy of Interpersonal Psychotherpay for Depressed Adolescents	Depression	IPT
1999	Silverman et al	Treating Anxiety Disorders in Children With Group Cognitive-Behavioral Therapy: A Randomized Clinical Trial	Anxiety	GCBT
1999	Silverman et al	Contingency Management, Self-Control, and Education Support in the Treatment of Childhood Phobic Disorders: A Randomized Clinical Trial	Phobic Disorders	cont. management, cog. self-control, ed. support
2000	Beidel et al	Behavioral Treatment of Childhood Social Phobia	Social Phobia	Behavioral Treatment
2000	Bernstein et al	Imipramine Plus Cognitive-Behavioral Therapy in the Treatment of School Refusal	School Refusal	Imipramine
2000	Flannery-Schroeder and Kendall	Group and Individual Cognitive-Behavioral Treatments for Youth with Anxiety Disorders: A randomized Clinical Trial	Anxiety	CBT, CBGT
2000	Hayward et al	Cognitive-Behavioral Group Therapy for Social Phobia in Female Adolescnts: Results of a Pilot Study	Social Phobia	CBGT
2001	Kendall et al	Comorbidity in Childood Anxiety Disorders and Treatment Outcome	Anxiety	CBT (Comorbidity)
2001	RUPP Group	Fluvoxamine for the Treatment of Anxiety Disorders in Children and Adolescents	Anxiety	Fluvoxamine
2001	Rynn et al	Placebo-Controlled Trial of Sertraline in the Treatment of Children with Generalized Anxiety Disorder	Anxiety	Sertraline

2001	Thompson et al	Evaluation of Indicated Suicide Risk Prevention Approaches for Potential High School Dropouts	Suicide	CARE, CAST
2002	Clarke et al	Group Cognitive-Behavioral Treatment for Depressed Adolescent Offspring of Depressed Parents in a Health Maintenance Organization	Depression	GCBT vs usual care
2002	DelBello et al	A Double-Blind, Randomized, Placebo-Controlled Trial of Quetiapine as Adjunctive Treatment for Adolescent Mania	Bipolar	Quetiapine
2002	Emslie et al	Fluoxetine for Acute Treatment of Depression in Children and Adolescents: A Placebo-Controlled, Randomized Clinical Trial	Depression	Fluoxetine
2003	Birmaher et al	Fluoxetine for the Treatment of Childhood Anxiety Disorders	Anxiety	Fluoxetine
2004	Mufson et al	A Randomized Effectiveness Trial of Interpersonal Psychotherapy for Depressed Adolescents	Depression	IPT
2004	TADS Team	Fluoxetine, Cognitive-Behavioral Therapy, and Their Combination for Adolescents With Depression	Depression	CBT, Fluoxetine, Both
2004	Wagner et al	A Randomized, Placebo-Controlled Trial of Citalopram for the Treatment of Major Depression in Children and Adolescents	Depression	Citalopram

Table 2. Follow-up RCT's Reviewed (1994-2005)

Year	Author(s)	Title	Disorder	Treatment	Original Study
1998	Brent et al	Predictors of Treatment Efficacy in a Clinical Trial of Three Psychosocial Treatments for Adolescent Depression	Depression	Psychosocial Treatments	Brent 1997
1998	Emslie et al	Fluoxetine in Child and Adolescent Depression: Acute and Maintenance Treatment	Depression	Fluoxetine	Emslie 1997
1998	Renaud et al	Rapid Response to Psychosocial Treatment for Adolescent Depression: A Two-Year Follow-up	Depression	Psychosocial Treatments	Brent 1997
1999	Brent et al	A Clinical Trial for Adolescent Depression: Predictors of Additional Treatment in the Acute and Follow-up Phases of the Trial	Depression		Brent 1997
1999	Kowatch et al	Prediction of response to Fluoxetine and placebo in children and adolescents with major depression: a hypothesis generating study	Depression	Fluoxetine	Emslie 1997
2000	Bernstein et al	Imipramine Compliance in Adolescents	School Refusal	Imipramine	Bernstein 2000
2000	Birmaher et al	Clinical Outcome After short-Term Psychotherapy for Adolescents With Major Depressive Disorder	Depression	Psychotherapy	Brent 1997
2000	Kolko et al	Cognitive and Family Therapies for Adolescent Depression: Treatment Specificity, Mediation, and Moderation	Depression	CBT, SBFT, NST	Brent 1997
2003	Layne et al	Predictors of Treatment Response in Anxious-Depressed Adolescents with School Refusal	School Refusal	CBT + Imipramine vs Placebo +Imipramine	Bernstein 2000
2003	RUPP Group	Searching for Moderators and Mediators of Pharmacological Treatment Effects in Children and Adolescents with Anxiety Disorders	Anxiety	Fluvoxamine	RUPP 2001
2004	Emslie et al	Fluoxetine Treatment for Prevention of Relapse of Depression in Children and Adolescents: A Double-Blind, Placebo-Controlled Study	Depression	Fluoxetine	Emslie 2002

2004	Kendall et al	Child Anxiety Treatment: Outcomes in Adolescents and Impact on Substane Use and Depression at 7.4-Year Follow-Up	Anxiety	CBT	Kendall 1997
2005	TADS Team	The Treatment for Adolescents With Depression Study (TADS): Demographic and Clinical Characteristics	Depression		TADS 2004

Table 3. Minority Representation (by %) in Original Trials Reviewed

Year	Author(s)	Disorder	Treatment	N	% Minority	% Caucasian	% African-American	% Latino	% Asian	% Native American	% Mixed	% Minority or Other
1994	Black and Uhde	Selective Mutism	Fluoxetine	15	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
1994	Graae et al	Anxiety	Clonazepam	12	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1994	Kendall et al.	Anxiety	CBT	47	24.0%	76.0%	24.0%	0.0%	0.0%	0.0%	0.0%	0.0%
1995	Clarke et al.	Depression	GCBT	150	7.3%	92.5%	0.0%	0.0%	0.0%	0.0%	0.0%	7.3%
1996	Kye et al	Depression	Amitriptyline	31	25.8%	74.2%	16.1%	0.0%	0.0%	0.0%	0.0%	9.7%
1996	Treadwell and Kendall	Anxiety	CBT	151	33.5%	66.5%	33.5%	0.0%	0.0%	0.0%	0.0%	0.0%
1997	Brent et al	Major Depression	CBT, SBFT, NST	107	16.8%	83.2%	0.0%	0.0%	0.0%	0.0%	0.0%	16.8%
1997	Emslie et al	Depression	Fluoxetine	96	20.8%	79.2%	0.0%	0.0%	0.0%	0.0%	0.0%	20.8%
1997	Kendall et al	Anxiety	CBT	94	14.9%	85.2%	5.6%	2.0%	3.4%	0.0%	0.0%	4.4%
1997	Sallee et al	Depression	Clomipramine	16	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
1997	Weisz et al	Depression	Prim & Sec Control Enhancement Training	48	37.5%	62.5%	0.0%	0.0%	0.0%	0.0%	0.0%	37.5%
1998	Ackerson et al	Depression	Cognitive Bibliotherapy	22	36.4%	63.6%	27.3%	0.0%	0.0%	0.0%	9.1%	0.0%
1998	Birmaher et al	Major Depression	Amitriptyline	27	11.1%	88.9%	11.1%	0.0%	0.0%	0.0%	0.0%	0.0%
1998	Geller et al	Bipolar	Lithium	25	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
1998	Geller et al	Depression	Lithium	30	3.3%	96.7%	0.0%	0.0%	0.0%	0.0%	0.0%	3.3%
1998	Klein et al	Depression	Desipramine	45	42.2%	57.8%	8.9%	26.7%	2.2%	0.0%	0.0%	4.4%
1998	Lamb et al	Depression	School-based CBT	41	4.9%	95.1%	0.0%	4.9%	0.0%	0.0%	0.0%	0.0%

1998	Last et al	School Refusal	CBT	47	10.6%	89.4%	4.3%	6.4%	0.0%	0.0%	0.0%	0.0%
1999	Clarke et al	Depression	GCBT, GCBT + parent group; + "Booster" sessions	96	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
1999	Mufson et al	Depression	IPT	48	70.9%	29.2%	0.0%	70.9%	0.0%	0.0%	0.0%	0.0%
1999	Silverman et al	Anxiety	GCBT	56	53.6%	46.4%	0.0%	46.4%	0.0%	0.0%	0.0%	7.1%
1999	Silverman et al	Phobic Disorders	cont. management, cog. self-control, ed. support	81	38.3%	61.7%	0.0%	35.8%	0.0%	0.0%	0.0%	2.5%
2000	Beidel et al	Social Phobia	Behavioral Treatment	50	30.0%	70.0%	22.0%	4.0%	0.0%	0.0%	4.0%	0.0%
2000	Bernstein et al	School Refusal	Imipramine	63	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
2000	Flannery-Schroeder and Kendall	Anxiety	CBT, CBGT	37	10.8%	89.2%	0.0%	0.0%	0.0%	0.0%	0.0%	10.8%
2000	Hayward et al	Social Phobia	CBGT	33	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**	**NR**
2001	Kendall et al	Anxiety	CBT (Comorbidity)	165	15.2%	84.8%	15.2%	0.0%	0.0%	0.0%	0.0%	0.0%
2001	RUPP Group	Anxiety	Fluvoxamine	128	36.7%	63.3%	7.0%	18.8%	0.0%	0.0%	0.0%	10.9%
2001	Rynn et al	Anxiety	Sertraline	22	19.0%	81.0%	0.0%	0.0%	0.0%	0.0%	0.0%	19.0%
2001	Thompson et al	Suicide	CARE, CAST	460	51.0%	48.9%	19.0%	10.0%	18.0%	4.0%	0.0%	0.0%
2002	Clarke et al	Depression	GCBT vs usual care	88	9.1%	90.9%	0.0%	0.0%	0.0%	0.0%	0.0%	9.1%

2002	DelBello et al	Bipolar	Quetiapine	30	16.7%	83.3%	0.0%	0.0%	0.0%	0.0%	0.0%	16.7%
2002	Emslie et al	Depression	Fluoxetine	219	17.8%	82.2%	6.4%	5.9%	0.5%	0.0%	0.0%	5.0%
2003	Birmaher et al	Anxiety	Fluoxetine	74	4.1%	95.9%	0.0%	0.0%	1.4%	0.0%	2.7%	0.0%
2004	Mufson et al	Depression	IPT	63	71.4%	28.6%	0.0%	71.4%	0.0%	0.0%	0.0%	0.0%
2004	TADS Team	Depression	CBT, Fluoxetine, Both	439	26.2%	73.8%	12.5%	8.9%	0.0%	0.0%	0.0%	4.8%
2004	Wagner et al	Depression	Citalopram	174	23.0%	77.0%	0.0%	0.0%	0.0%	0.0%	0.0%	23.0%
NR = Not reported.												