Generalizability of Clinical Trial Results for Adolescent Major Depressive Disorder

Carlos Blanco, MD, PhD,[a] Nicolas Hoertel, MD, MPH,[b,c,d] Silvia Franco, MD,[e] Mark Olfson, MD, MPH,[e] Jian-Ping He, MSc,[f] Saioa López, MD,[g] Ana González-Pinto, MD, PhD,[g] Frédéric Limosin, MD, PhD,[b,c,d] Kathleen R. Merikangas, PhD[f]

abstract

BACKGROUND: Although there have been a number of clinical trials evaluating treatments for adolescents with major depressive disorder (MDD), the generalizability of those trials to samples of depressed adolescents who present for routine clinical care is unknown. Examining the generalizability of clinical trials of pharmacological and psychotherapy interventions for adolescent depression can help administrators and frontline practitioners determine the relevance of these studies for their patients and may also guide eligibility criteria for future clinical trials in this clinical population.

METHODS: Data on nationally representative adolescents were derived from the National Comorbidity Survey: Adolescent Supplement. To assess the generalizability of adolescent clinical trials for MDD, we applied a standard set of eligibility criteria representative of clinical trials to all adolescents in the National Comorbidity Survey: Adolescent Supplement with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnosis of MDD (N = 592).

RESULTS: From the overall MDD sample, 61.9% would have been excluded from a typical pharmacological trial, whereas 42.2% would have been excluded from a psychotherapy trial. Among those who sought treatment (n = 412), the corresponding exclusion rates were 72.7% for a pharmacological trial and 52.2% for a psychotherapy trial. The criterion leading to the largest number of exclusions was "significant risk of suicide" in both pharmacological and psychotherapy trials.

CONCLUSIONS: Pharmacological and, to a lesser extent, psychotherapy clinical trials likely exclude most adolescents with MDD. Careful consideration should be given to balancing eligibility criteria and internal validity with applicability in routine clinical care while ensuring patient safety.

[a]*Division of Epidemiology, Services, and Prevention Research, National Institute on Drug Abuse, Bethesda, Maryland;* [f]*Genetic Epidemiology Branch, Intramural Research Program, National Institute of Mental Health, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland;* [b]*Paris Descartes University, Pôles de recherche et d'enseignement supérieur Sorbonne Paris Cité, Paris, France;* [c]*Department of Psychiatry, Assistance Publique-Hôpitaux de Paris, Hôpital Corentin-Celton, Issy-les-Moulineaux, France;* [d]*Institut national de la santé et de la recherche médicale unité mixte de recherche 894, Psychiatry and Neurosciences Center, Paris, France;* [e]*Department of Psychiatry, New York State Psychiatric Institute and Columbia University, New York, New York; and* [g]*Hospital Universitario de Alava (Santiago), Centre for Biomedical Research in Mental Health Network, Vitoria, Spain*

The views and opinions expressed in this report are those of the authors and should not be construed to represent the views of any of the sponsoring organizations, agencies, or the US government.

Drs Blanco and Merikangas conceptualized and designed the study and drafted the initial manuscript; Dr Hoertel conceptualized and designed the study, collected all eligibility criteria

WHAT'S KNOWN ON THIS SUBJECT: Over the last 2 decades, in several studies, researchers have evaluated treatments to guide clinical management of adolescents with depression. However, the generalizability of these clinical trial samples to the broader population of adolescents with depression is unknown.

WHAT THIS STUDY ADDS: We estimated the generalizability of clinical trials of pharmacological and psychotherapy interventions for adolescent depression. An understanding of the generalizability of these interventions is important to help administrators and front-line practitioners determine the relevance of these studies for their patients.

To cite: Blanco C, Hoertel N, Franco S, et al. Generalizability of Clinical Trial Results for Adolescent Major Depressive Disorder. *Pediatrics.* 2017;140(6):e20161701

Major concerns in any randomized controlled trial (RCT) include ensuring the validity of the data being collected as well as the protection of the rights and safety of study participants. In response to these concerns, researchers conducting RCTs apply inclusion and exclusion criteria to ensure that studies meet ethical standards, that participation in them is safe, and that participants have the clinical and sociodemographic characteristics needed to answer the research question. In particular, eligibility criteria are used to ensure participants' safety, prevent exploitation of vulnerable persons, reduce study costs and attrition rate, allow for adequate evaluation of the effect of a treatment on a specific disorder and increase the likelihood of generating reliable and reproducible results, and comply with guidelines of regulatory agencies.[1–7] However, authors of previous research[1–7] suggest that the use of restrictive eligibility criteria may result in research samples that often do not adequately represent the range of patients seen in routine clinical care. As concerns have emerged regarding the use of stringent exclusion criteria in clinical trials, there has been growing interest in quantifying the generalizability of clinical trial results to the broader target population[8] and in more optimally balancing internal validity (ie, the extent to which a causal conclusion based on a study is warranted) and external validity (ie, the applicability of clinical trial results to routine clinical settings) while ensuring participant safety.[9–12]

In several influential studies over the last 2 decades, researchers have evaluated treatments to guide the clinical management of adolescents with major depressive disorder (MDD),[13] but the generalizability of these RCT samples to the broader population of adolescents with MDD is unknown. Examining the generalizability of RCTs of pharmacological and psychotherapy interventions for adolescent depression can help administrators and frontline practitioners determine the relevance of these studies for their patients. An understanding of the generalizability of clinical trials might also assist research funding agencies in identifying gaps in knowledge and help guide eligibility criteria for future clinical trials in this clinical population.

In this study, we apply exclusion criteria commonly used in adolescent pharmacological and psychotherapy clinical trials for MDD to a large, nationally representative adolescent population sample of the United States to assess the generalizability of the criteria to adolescents with MDD and to a subsample of adolescents seeking treatment for depression.

METHODS

Sample

Data were drawn from the National Comorbidity Survey: Adolescent Supplement (NCS-A), a nationally representative, face-to-face survey of 10 123 adolescents aged 13 to 18 years conducted between February 2001 and January 2004 in the continental United States and described in detail elsewhere.[14–17] The survey was administered by the professional interview staff of the Institute for Social Research at the University of Michigan. The NCS-A was conducted in a dual-frame sample that included a household subsample and a school subsample. These recruitment and consent procedures received full human subjects review and approval from the human subjects committees of Harvard Medical School and the University of Michigan.

The overall NCS-A adolescent response rate after combining the 2 subsamples was 82.9%. One parent or parent surrogate of each participant was asked to complete a self-administered questionnaire (SAQ) that contained informant questions about the adolescent's developmental history and mental health. The full SAQ was completed by 6491 parents. In the present report, we focus on the 6483 adolescent-parent pairs for which complete data are available from both adolescents and parents. From this group, we selected all participants with a 12-month *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) diagnosis of MDD ($N = 592$) and a subsample who sought mental health treatment ($n = 412$).

DSM-IV Diagnostic Interview

Lifetime and 12-month psychiatric diagnoses were made according to DSM-IV[18] criteria by using a modified version of the World Health Organization Composite International Diagnostic Interview (CIDI) 3.0, a fully structured interview administered by trained lay interviewers.[19] The CIDI was modified to enhance the wording and appropriateness of the instrument for the assessment of adolescents.[20,21] Suicidal ideation was assessed by asking, "Have you ever seriously thought about killing yourself?" Adolescents who endorsed lifetime suicidal ideation were questioned about lifetime suicide attempts by asking, "Have you ever attempted suicide?"

Parents who completed the SAQ provided full DSM-IV diagnostic information about MDD, whereas those completing the abbreviated SAQ only reported on attention-deficit/hyperactivity disorder. Information from both the parent and adolescent were combined for major depressive episode (MDE) and behavioral problems and classified as positive if either informant endorsed the diagnostic criteria.[22,23] Definitions of all psychiatric disorders followed DSM-IV criteria, and diagnostic

hierarchy rules were applied for every disorder, with the exception of oppositional defiant disorder and substance use disorders. Psychiatric disorder diagnoses derived from the modified CIDI (including MDD) had good concordance with a clinical reappraisal subsample.[15] There was good concordance between the CIDI Version 3.0 diagnoses from the NCS-A and from the Schedule for Affective Disorders and Schizophrenia for School-Age Children,[24] including under the receiver operating characteristic curve of 0.88 for any anxiety disorder, 0.89 for any mood disorder, 0.84 for any disruptive behavior disorder, and 0.94 for any substance disorder.

Clinical Trials' Exclusion Criteria

Exclusion criteria commonly used in adolescent pharmacological and psychotherapy RCTs for MDD were applied to the full NCS-A sample of individuals with self-report and parental information who met the criteria for the current DSM-IV diagnosis of MDD. The same exclusion criteria were applied to the subsample of adolescents who sought treatment of MDD to investigate potential differences in eligibility between treatment-seeking and non–treatment-seeking adolescents with MDD.[1]

We collected the exclusion criteria from adolescent clinical trials for MDD included in 2 recent meta-analyses examining the effects of pharmacological[25] and psychotherapy[26] treatments for adolescents with MDD. Only trials published after 1997 were included in our analyses because journals strengthened their policies after this date, requiring the reporting of exclusion criteria.[27] The analysis of exclusion criteria included all 34 trials published after 1997 in the meta-analysis of psychotherapy treatments and all 25 trials published after 1997 in the meta-analysis of pharmacological treatments.

TABLE 1 Exclusion Criteria in 25 Clinical Trials Examining the Effects of Pharmacological Treatments for Adolescents With MDD

Exclusion Criteria, Ranked by Frequency[a]	Studies Using the Criteria, Reference No.	No. of Studies Using the Criteria (25)
1. Lifetime psychotic features	29–51	23
2. Lifetime bipolar I or II disorder	29–33·35–52	23
3. Currently taking any psychotropic medication	30–36·38–45·47–52	21
4. Alcohol or drug abuse and/or dependence (within the last 6 mo)	29–32·34·35·37–43·45–50·52	20
5. Significant risk of suicide[b]	29–33·35·38–49·52	20
6. Any current significant physical condition	30–32·34–41·43·44·46·47·49·51	17
7. Developmental disorder or mental deficiency	30·32–35·37–40·42·45·47–50·52	17
8. Pregnant, breastfeeding, or sexually active without contraception	31·34·35·38·39·41–45·47–52	16
9. Lifetime eating disorder	29·34·37–39·41·42·44–50	14
10. Lifetime obsessive-compulsive disorder	29·31·32·35·41·42·44–47·49·51	12
11. Current panic disorder	31·32·34·35·41·42·44·47·49·51	10
12. Conduct disorder	30·35·41·42·47–49·51·52	9
13. Currently receiving psychotherapy	30·35·38–40·42·48·49·52	9
14. Neurologic condition	32·34·38·39·44·45·47·50	8
15. Current generalized anxiety disorder	31·32·34·35·42·47·49	7
16. Attention-deficit/hyperactivity disorder	30·31·42·47–50	7
17. Current social anxiety disorder	31·32·35·42·47·49	6
18. Current specific phobia	31·32·35·42·47·49	6
19. Current dysthymia	31·32·35·42·47·49	6
20. Severe personality disorder	38·39·42·47–49	6
21. Current posttraumatic stress disorder	35·42·45·47·49	5
22. Oppositional defiant disorder	30·42·48·49	4
23. Severe malnutrition	47·49	2
24. Low English proficiency	52	1

[a] Derived from the review of 25 clinical trials (method described in the article).
[b] Of the 20 studies using this criterion, 4 specified "any previous suicide attempt," 3 "any previous suicide attempt or any suicide plan," 3 "any previous suicide attempt or suicidal ideation," and 10 did not detail this criterion.

Two coders (S.F. and N.H.) independently collected all eligibility criteria from the clinical trials (Tables 1 and 2). Intercoder reliability was adequate[28] (intraclass correlation coefficient, 0.84; 95% confidence interval, 0.68–0.90). Disagreement was resolved by consensus. The median number of exclusion criteria applied was 11 for the pharmacological clinical trials and 4 for the psychotherapy clinical trials. To estimate the representativeness of a typical pharmacological and psychotherapy clinical trial with traditional exclusion criteria, we applied, respectively, the 11 and the 4 most commonly used exclusion criteria to adolescents in the NCS-A who met the criteria for past-year MDD (Tables 3 and 4).

The percentage of participants excluded was estimated from responses to the modified version of the CIDI 3.0.[19] The criteria "lifetime bipolar I or II disorder," "lifetime eating disorder," and "past-year panic disorder" were diagnosed by using DSM-IV criteria. The criterion "current or past 6-month drug or alcohol abuse and/or dependence" was defined as having a DSM-IV diagnosis of dependence or abuse on alcohol or drug within the past 12 months. The criterion "significant risk of suicide" was considered met if the adolescent ever attempted suicide. The criterion "current psychotropic medication" was considered present if adolescents reported taking psychotropic medication within the last 12 months. "Developmental disorder" was assessed from parents' reports of their child's behavior and developmental history. The criterion "significant physical condition" was indexed by a series of self-report

TABLE 2 Exclusion Criteria in 34 Clinical Trials Examining the Effects of Psychological Treatments for Adolescents With MDD

Exclusion Criteria Present in >10% of the Studies, Ranked by Frequency[a]	Studies Using the Criteria, Reference No.	No. of Studies Using the Criteria (34)
1. Lifetime psychotic features	53–74	22
2. Lifetime bipolar I or II disorder	53–58·60–68·71·72·74·75	19
3. Current psychoactive medication	55·57·58·60·61·63·65·66·68·70·72·73·75–77	15
4. Significant risk of suicide[b]	53·55–58·60–63·66·73·78–80	14
5. Currently receiving psychotherapy	55·57·58·60·61·63·65·70·72·73·75–77·79	14
6. Alcohol or drug abuse and/or dependence (within the last 6 mo)	56–58·60–66·70–72·74	14
7. Developmental disorder or mental deficiency	57·60·62·63·66·67·69·72·76·80	10
8. Conduct disorder	53–55·57·58·61·62·72·78	9
9. Lifetime obsessive-compulsive disorder	53·54·61·63–65·71·74	8
10. Current panic disorder	53·54·62–65·71·72	8
11. Any current significant physical condition	56·60·61·65·66·72·74	7
12. Current dysthymia	53·55·63–65·71	6
13. Current generalized anxiety disorder	62–65·71·72	6
14. Need of hospitalization	55·56·62·66·69	5
15. Current social anxiety disorder	63–65·71	4
16. Current specific phobia	63–65·71	4
17. Neurologic condition	58·62·66	3
18. Lifetime eating disorder	61·66·74	3
19. Oppositional defiant disorder	53·54·78	3
20. No parental history of depression or dysthymia	81·82	2
21. Ongoing physical or sexual abuse	66·74	2
22. Current posttraumatic stress disorder	53·54	2
23. Low English proficiency	59·63	2
24. Attention-deficit hyperactivity disorder	53·54	2
25. Litigation	58·59	2
26. Charges of first degree assault, robbery, homicide or rape	57·59	2
27. Pregnancy or breastfeeding	74	1
28. Aggressive behavior	57	1
29. Cluster B personality disorders	56	1

[a] Derived from the review of 34 clinical trials (method described in the article).
[b] Of the 15 studies using this criterion, 3 specified "any previous suicide attempt," 3 "suicidal ideation," and 9 did not detail this criterion.

questions regarding the presence of HIV/AIDS, cancer, diabetes, heart problems, and epilepsy and/or seizure in the past year or parental report of an adolescent heart problem, frequent high fever, and epilepsy and/or seizure. Information to approximate the criteria "lifetime psychotic features," "pregnant, breastfeeding, or sexually active without contraception," and "lifetime obsessive-compulsive disorder" was not available in the NCS-A.

Among respondents with current MDD, treatment seeking was defined by report of any treatment of emotional and behavioral problems in the mental health specialty sector, general medical sector, or school services system during the year preceding the interview.

Statistical Analyses

We first defined the percentages (and their SEs) of survey participants with MDD who would have been excluded by applying each one of the exclusion criteria in clinical trials for MDD. Because individuals could have been excluded by more than 1 criterion, we also calculated the overall percentage of subjects who would have been excluded by the simultaneous application of all available criteria. We conducted these analyses for all participants with a 12-month DSM-IV diagnosis of MDE (N = 592) and for the subsample who sought treatment (n = 412). Analyses were performed by using SUDAAN 10.0.1[83] (Research Triangle Institute, Research Triangle Park, NC) to take into account the complex survey design. Wald statistics were used to examine potential differences between adolescents who would have been included in a typical clinical trial for MDD and those who would have been excluded. Significance tests were calculated by using Wald χ^2 tests based on coefficient variance-covariance matrices that were adjusted for design effects by using the Taylor series method. Statistical significance was based on 2-sided design-based tests evaluated at a level of significance of .05.

Supplementary Analyses

To determine if the median number of exclusion criteria and the generalizability rate differed between recent and older pharmacological and psychotherapy clinical trials for MDD, we applied the method described above separately for recent trials (ie, published after 2006) and those older (ie, published in 2006 or before).

RESULTS

In the full sample of 592 participants who met DSM-IV criteria for MDE, 61.9% (SE = 3.6) would have been excluded by at least 1 of the 8 most common and operationalizable criteria in pharmacological trials, and 72.7% (SE = 3.2) would have been excluded from the subsample of 412 participants who sought treatment (Table 3). In both the full sample and the treatment seeking subsample, the criterion leading to the largest number of exclusions was "significant risk of suicide." The criteria "past-year alcohol or drug abuse and/or dependence" and "past-year use of psychotropic medication" also

TABLE 3 Estimated Percentage of Adolescents With 12-Month MDE in NCS-A Excluded by Traditional Eligibility Criteria in 25 Adolescent Pharmacological Trials for MDD

Exclusion Criteria	12-mo DSM-IV MDE Cases						Group Difference (Treatment-Seeking Versus Non–Treatment Seeking)
	Total (N = 592)		Treatment-Seeking Group[a] (n = 412)		Non–Treatment Seeking (n = 180)		
	n	% (SE)	n	% (SE)	n	% (SE)	Wald χ^2_1 (P)
1. Lifetime psychotic features				NA			—
2. Lifetime bipolar I or II disorder	62	11.21 (2.27)	51	12.83 (2.83)	11	6.80 (3.05)	1.8 (.176)
3. Past-year use of psychotropic medication	112	19.73 (2.75)	109	25.95 (3.09)	3	2.75 (1.72)	15.9 (.000)
4. Past-year alcohol or drug abuse and/or dependence	107	24.47 (3.43)	90	29.18 (4.13)	17	11.62 (4.59)	5.1 (.023)
5. Significant risk of suicide[b]	100	25.34 (4.94)	91	32.74 (5.86)	9	5.15 (2.20)	19.6 (.000)
6. Past-year significant physical condition[c]	52	8.89 (1.69)	43	11.07 (2.24)	9	2.95 (1.25)	8.5 (.003)
7. Developmental disorder[d]	2	0.16 (0.13)	2	0.22 (0.18)	0	0.00 (0.00)	—
8. Pregnant, breastfeeding, or sexually active without contraception				NA			—
9. Lifetime eating disorder	60	13.10 (3.38)	49	15.81 (4.39)	11	5.69 (2.47)	3.7 (.054)
10. Lifetime obsessive-compulsive disorder				NA			—
11. Past-year panic disorder	41	5.82 (1.51)	33	6.39 (1.96)	8	4.28 (2.75)	0.3 (.592)
At least 1 criterion	325	61.88 (3.63)	270	72.71 (3.16)	55	32.31 (5.71)	32.4 (.000)

Percentages are weighted values. NA, not available in NCS-A; —, not applicable.

[a] Defined as receiving any treatment of emotional and behavioral problems in the mental health specialty sector, general medical sector, or school services system during the year preceding the interview.

[b] Defined as having a lifetime history of suicide attempt.

[c] Approximated by series of questions on 12-mo diabetes, HIV/AIDS, and cancer diagnosis (reported by adolescents); frequent high fever (reported by parents); and heart problems and epilepsy and/or seizure (reported by adolescents or parents).

[d] Approximated from parent's reports about child's developmental history.

TABLE 4 Estimated Percentage of Adolescents With 12-Month MDE in NCS-A Excluded by Traditional Eligibility Criteria in 34 Adolescent Psychological Trials for MDD

Exclusion Criteria	12-mo DSM-IV MDE Cases						Group Difference (Treatment-Seeking Group Versus Non–Treatment Seeking)
	Total (N = 592)		Treatment-Seeking Group[a] (n = 412)		Non–Treatment Seeking (n = 180)		
	n	% (SE)	n	% (SE)	n	% (SE)	Wald χ^2_1 (P)
1. Lifetime psychotic features				NA			—
3. Lifetime bipolar I or II disorder	62	11.21 (2.27)	51	12.83 (2.83)	11	6.80 (3.05)	1.8 (.176)
3. Past-year use of psychotropic medication	112	19.73 (2.75)	109	25.95 (3.09)	3	2.75 (1.72)	15.9 (.000)
4. Significant risk of suicide[b]	100	25.34 (4.94)	91	32.74 (5.86)	9	5.15 (2.20)	19.6 (.000)
At least 1 criterion	215	42.15 (4.71)	192	52.20 (4.95)	23	14.70 (3.84)	30.8 (.000)

Percentages are weighted values. NA, not available in NCS-A; —, not applicable.

[a] Defined as receiving any treatment of emotional and behavioral problems in the mental health specialty sector, general medical sector, or school services system during the year preceding the interview.

[b] Defined as having a lifetime history of suicide attempt.

excluded a substantial proportion of respondents.

In psychotherapy trials, the percentage of adolescents excluded by at least 1 of the 3 most common and operationalizable criteria was 42.2% (SE = 4.7) in the full sample and 52.2% (SE = 5.0) in the treatment-seeking subsample (Table 4). In both the full sample and the treatment-seeking subsample, the criterion resulting in the largest number of exclusions was "significant risk of suicide."

The overall exclusion rate was significantly higher in participants who sought treatment than in those who did not (P < .001 for pharmacological and psychotherapy trials). The prevalence of 12-month alcohol or drug abuse and/or dependence, significant risk of suicide, use of psychotropic medication, and significant medical conditions within the past year were significantly higher in treatment seekers compared with non–treatment seekers in pharmacological trials (Table 3). As compared with the non–treatment-seeking subsample, the treatment-seeking sample in psychological clinical trials also had a significantly higher prevalence of 12-month use of psychotropic medication and a significantly higher proportion of adolescents at risk for suicide (Table 4).

The overall exclusion rate was within the same range in older

and recent pharmacological trials (60.2% [SE = 3.6] vs 65.6% [SE = 3.7] with a maximum number of exclusion criteria that could be approximated of 7 out of 11 and 8 out of 11, respectively), and the median number of exclusion criteria was identical (ie, 11) (Supplemental Tables 5 and 6). By contrast, the median number of exclusion criteria and the overall exclusion rate were substantially lower in recent than in older psychotherapy trials (3 vs 5; 32.7% [SE = 4.7] vs 45.6% [SE = 4.4] with a maximum number of exclusion criteria that could be approximated of 2 out of 3 and 3 out of 5, respectively) (Supplemental Tables 7 and 8).

DISCUSSION

In a typical pharmacological trial for MDD, >6 out of 10 adolescents with MDD in the general population and >7 out of 10 among those seeking treatment would have been excluded by at least 1 commonly used study exclusion criteria. In a typical psychotherapy trial for MDD, >4 of 10 adolescents with MDD in the general population and >5 of 10 among those seeking treatment of MDD would have been excluded by at least 1 commonly used study exclusion criteria. Consistent with previous studies in adult samples,[2,84–88] we found that exclusion criteria commonly used in adolescent clinical trials for MDD exclude a substantial proportion of adolescents from participation, particularly those seeking treatment. The representativeness of psychotherapy trials for MDD tended to be higher in recent years, whereas that of pharmacological trials for MDD did not appear to increase over time.

Adolescents with MDD commonly present with comorbid medical and psychiatric disorders,[16,88–93] which would frequently lead to their exclusion from typical MDD clinical trials. In our findings, we suggest that clinical trial results examining the effects of pharmacological and psychotherapy treatments in adolescents with MDD may have limited generalizability to community settings because they tend to include "pure" rather than "typical" patients.[94] The higher overall exclusion rate found in typical pharmacological trials compared with typical psychotherapy trials is consistent with recent findings in adults[87] and may be partially explained by the larger number of exclusion criteria applied in pharmacological trials.

Pharmacologic trials excluded >60% of the adolescents with MDD. This proportion is comparable to studies in which researchers have assessed the generalizability of pharmacological trials in adults.[3,6,88] The use of exclusion criteria in response to concerns about patient safety (eg, pregnancy, significant medical conditions), study feasibility, or interpretability of results is justified.[95] However, the use of other criteria may mostly reflect a tradition that has evolved over time within a particular research area,[96,97] resulting in a progressive, unnecessary narrowing of the population of eligible patients (eg, substance use disorders or anxiety disorders).[98] Our results suggest that this may be particularly true for pharmacological trials whose generalizability did not increase in recent years, in contrast to psychotherapy trials. Those trials might prioritize the inclusion of narrowly defined uncomplicated subjects in an effort to maximize treatment effects. Indeed, comorbid psychiatric disorders and medical conditions are an important source of heterogeneity in treatment response,[99–101] and authors of previous research suggest that patients with psychiatric or general medical comorbidities tend to have poorer treatment outcomes.[6,101–104] This incentive may be greater because the current Food and Drug Administration labeling does not reflect the study subject selection process. Specifically, the Food and Drug Administration indication drawn from these trials are for "adolescent major depressive disorder" and not for "uncomplicated adolescent major depressive disorder." There is an inherent tension between the wish of investigators and manufacturers to obtain positive results in their trials and the clinical interests of patients and their providers who seek information from broadly representative studies. In this context, there is a need to carefully consider the advantages and disadvantages of applying each exclusion criterion that is not dedicated to increase patient safety and to balance internal and external validity.

We found that the criterion resulting in the largest number of exclusions in pharmacological and psychotherapy trials was "significant risk of suicide." Given the public health importance of suicide prevention in young people, the exclusion of adolescents with a significant risk of suicide is an especially important example of the tension between the need for more inclusive eligibility criteria to better inform clinical practice and the constraints (such as the stringent safety standards applied to clinical research) that limit the application of those broader criteria.[105,106] To address this issue, a potential approach may be to establish efficacy of a specific pharmacological or psychotherapy intervention in a subset of adolescents with MDD and a low risk of suicide and then seek to evaluate its effectiveness in a subset of more vulnerable adolescents.

Application of the eligibility criteria to the treatment-seeking subsample excluded a significantly greater proportion of depressed adolescents from psychotherapy and pharmacological clinical trials

for MDD. Consistent with previous research with adults,[107–112] this suggests that individuals with a given disorder who seek treatment tend to have greater illness severity and more psychiatric and medical comorbidities than those who do not seek treatment. Furthermore, high rates of psychiatric and medical comorbidities may increase the perceived need for care, which in turn may influence treatment-seeking behavior in adolescents and their parents.[113]

For adolescent MDD treatment trials to adequately inform clinical practice, the eligibility fraction must be increased by a progressive broadening of eligibility criteria. However, having a heterogeneous treatment group can make analyses challenging. In our study, we identified several subgroups of adolescents typically excluded from trials (eg, those with substance use disorders or anxiety disorders). Conducting trials in these subpopulations may help inform clinical practice. In addition, developing integrated forms of pharmacotherapy and psychotherapy that target commonly cooccurring psychiatric disorders may yield more informative results for mental health care professionals and research funding agencies.[114,115]

The current study has several limitations. First, although the NCS-A items closely resemble the exclusion criteria, they do not precisely match them. For example, the 12-month time frame used in the NCS-A when assessing the presence of "alcohol or drug abuse and/or dependence within the last 6 months" could have led to an overestimation of exclusion rates. In addition, because most of the trials that used the criterion "significant suicide risk" did not detail it (ie, attempt, plan, ideation, etc), we operationalized "significant suicide risk" using NCS-A items of reporting a previous suicide attempt. Finally, most of the clinical trials included in this analysis did not detail the specific medical conditions used as exclusion criteria. Other conventions might have yielded different exclusion estimates. Second, 3 exclusion criteria were not available in the NCS-A, which likely led to an underestimation of the overall exclusion rates. Finally, the NCS-A participants were 13 to 18 years of age. Because children with MDD tend to have fewer psychiatric and general medical comorbidities than adolescents with MDD,[116] exclusion rates of clinical trials for MDD may be lower in children than adolescents.

CONCLUSIONS

Because clinical trials of adolescent MDD exclude adolescents with psychiatric and addictive disorders, significant medical conditions, suicide risk, and other characteristics, they have limited external validity. These studies represent important progress in the development of evidence-based treatments for adolescent MDD. However, our results support that careful consideration should be given to balancing eligibility criteria and adequate internal validity with applicability in routine clinical care while ensuring patient safety.

ABBREVIATIONS

CIDI: Composite International Diagnostic Interview
DSM-IV: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
MDD: major depressive disorder
MDE: major depressive episode
NCS-A, National Comorbidity Survey: Adolescent Supplement
RCT: randomized controlled trial
SAQ: self-administered questionnaire

from the clinical trials, and drafted the initial manuscript; Dr Franco collected all eligibility criteria from the clinical trials and reviewed and revised the manuscript; Ms He conducted the initial analyses; Drs Olfson, López, González-Pinto, and Limosin critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2016-1701

Accepted for publication Jul 31, 2017

Address correspondence to Nicolas Hoertel, MD, MPH, Department of Psychiatry, Corentin-Celton Hospital, 4 parvis Corentin Celton, 92130 Issy-les-Moulineaux, France. E-mail: nico.hoertel@yahoo.fr

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by the Intramural Research Program of the National Institute of Mental Health (ZIAMH002808), National Institutes of Health grants MH076051 and MH082773 (Drs Blanco and Olfson), and the New York State Psychiatric Institute (Drs Blanco, Hoertel, and Olfson). Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: Dr Blanco owns stock options in Eli Lilly and Company and Sanofi; Dr González-Pinto has received grants and served as consultant, advisor, or continuing medical education speaker for the following entities: Almirall, AstraZeneca, Cephalon, Eli Lilly, Bristol-Myers Squibb, GlaxoSmithKline, Janssen-Cilag, Jazz, Johnson & Johnson, Lundbeck, Merck, Otsuka, Pfizer, Servier, Sanofi-Aventis, Schering-Plough, Solvay, Centre for Biomedical Research in Mental Health Network, Carlos III Institute, Basque Government, Stanley Medical Research Institute, and Wyeth; Dr Limosin is a member of the

speakers and/or advisory boards for Janssen, Euthérapie, Lundbeck, and Roche; the other authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2017-3098.

REFERENCES

1. Blanco C, Olfson M, Okuda M, Nunes EV, Liu SM, Hasin DS. Generalizability of clinical trials for alcohol dependence to community samples. *Drug Alcohol Depend*. 2008;98(1–2):123–128
2. Blanco C, Olfson M, Goodwin RD, et al. Generalizability of clinical trial results for major depression to community samples: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2008;69(8):1276–1280
3. Hoertel N, López S, Wang S, González-Pinto A, Limosin F, Blanco C. Generalizability of pharmacological and psychotherapy clinical trial results for borderline personality disorder to community samples. *Personal Disord*. 2015;6(1):81–87
4. Humphreys K. A review of the impact of exclusion criteria on the generalizability of schizophrenia treatment research. *Clin Schizophr Relat Psychoses*. 2014;1–25
5. Humphreys K, Harris AH, Weingardt KR. Subject eligibility criteria can substantially influence the results of alcohol-treatment outcome research. *J Stud Alcohol Drugs*. 2008;69(5):757–764
6. Hoertel N, Le Strat Y, Blanco C, Lavaud P, Dubertret C. Generalizability of clinical trial results for generalized anxiety disorder to community samples. *Depress Anxiety*. 2012;29(7):614–620
7. Hoertel N, Le Strat Y, Lavaud P, Dubertret C, Limosin F. Generalizability of clinical trial results for bipolar disorder to community samples: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2013;74(3):265–270
8. Stevens J, Kelleher K, Greenhouse J, et al. Empirical evaluation of the generalizability of the sample from the multimodal treatment study for ADHD. *Adm Policy Ment Health*. 2007;34(3):221–232
9. Dzewaltowski DA, Estabrooks PA, Klesges LM, Bull S, Glasgow RE. Behavior change intervention research in community settings: how generalizable are the results? *Health Promot Int*. 2004;19(2):235–245
10. Hoertel N, Le Strat Y, Limosin F, Dubertret C, Gorwood P. Prevalence of subthreshold hypomania and impact on internal validity of RCTs for major depressive disorder: results from a national epidemiological sample. *PLoS One*. 2013;8(2):e55448
11. Hoertel N, Falissard B, Humphreys K, Gorwood P, Seigneurie AS, Limosin F. Do clinical trials of treatment of alcohol dependence adequately enroll participants with co-occurring independent mood and anxiety disorders? An analysis of data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Clin Psychiatry*. 2014;75(3):231–237
12. Hoertel N, Le Strat Y, De Maricourt P, Limosin F, Dubertret C. Are subjects in treatment trials of panic disorder representative of patients in routine clinical practice? Results from a national sample. *J Affect Disord*. 2013;146(3):383–389
13. Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN. Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database Syst Rev*. 2012;11:CD004851
14. Kessler RC, Avenevoli S, Costello EJ, et al. National comorbidity survey replication adolescent supplement (NCS-A): II. Overview and design. *J Am Acad Child Adolesc Psychiatry*. 2009;48(4):380–385
15. Kessler RC, Avenevoli S, Costello EJ, et al. Design and field procedures in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A). *Int J Methods Psychiatr Res*. 2009;18(2):69–83
16. Merikangas KR, He JP, Burstein M, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry*. 2010;49(10):980–989
17. Nock MK, Green JG, Hwang I, et al. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. *JAMA Psychiatry*. 2013;70(3):300–310
18. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994
19. Kessler RC, Ustün TB. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *Int J Methods Psychiatr Res*. 2004;13(2):93–121
20. Kessler RC, Merikangas KR. The National Comorbidity Survey Replication (NCS-R): background and aims. *Int J Methods Psychiatr Res*. 2004;13(2):60–68
21. Merikangas K, Avenevoli S, Costello J, Koretz D, Kessler RC. National comorbidity survey replication adolescent supplement (NCS-A): I. Background and measures. *J Am Acad Child Adolesc Psychiatry*. 2009;48(4):367–369
22. Cantwell DP, Lewinsohn PM, Rohde P, Seeley JR. Correspondence between adolescent report and parent report of psychiatric diagnostic data. *J Am Acad Child Adolesc Psychiatry*. 1997;36(5):610–619
23. Grills AE, Ollendick TH. Issues in parent-child agreement: the case of structured diagnostic interviews. *Clin Child Fam Psychol Rev*. 2002;5(1):57–83
24. Kessler RC, Avenevoli S, Green J, et al. National comorbidity survey replication adolescent supplement

(NCS-A): III. Concordance of DSM-IV/CIDI diagnoses with clinical reassessments. *J Am Acad Child Adolesc Psychiatry*. 2009;48(4):386–399

25. Cipriani A, Zhou X, Del Giovane C, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet*. 2016;388(10047):881–890
26. Zhou X, Hetrick SE, Cuijpers P, et al. Comparative efficacy and acceptability of psychotherapies for depression in children and adolescents: a systematic review and network meta-analysis. *World Psychiatry*. 2015;14(2):207–222
27. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *N Engl J Med*. 1997;336(4):309–315
28. Krippendorff K. Reliability in content analysis: some common misconceptions and recommendations. *Hum Commun Res*. 2004;30(3):411–433
29. Organon Pharmaceuticals USA, Inc. A multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study of Remeron in outpatient children and adolescents with major depressive disorder. 2001. Available at: www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM164066.pdf. Accessed May 20, 2016
30. Almeida-Montes LG, Friederichsen A. Treatment of major depressive disorder with fluoxetine in children and adolescents. A double-blind, placebo-controlled study [in Spanish]. *Psiquiatr Biologica*. 2005;12:198–205
31. Atkinson SD, Prakash A, Zhang Q, et al. A double-blind efficacy and safety study of duloxetine flexible dosing in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2014;24(4):180–189
32. Attari A, Moghaddam FY, Hasanzadeh A, Soltani M, Mahmoodi M. Comparison of efficacy of fluoxetine with nortriptyline in treatment of major depression in children and adolescents: a double-blind study. *J Res Med Sci*. 2006;11(1):24–30
33. Eli Lilly and Company. Clinical study summary: Study B1Y-MC-HCCJ. Fluoxetine: fluoxetine versus placebo in adolescent depressed patients. 2004. Available at: http://art45-paediatric-studies-docs.ema.europa.eu/GROUP F/Fluoxetine/fluoxetine B1Y-MC-HCCJ Clinical Study Summary.pdf. Accessed April 17, 2016
34. Braconnier A, Le Coent R, Cohen D; DEROXADO Study Group. Paroxetine versus clomipramine in adolescents with severe major depression: a double-blind, randomized, multicenter trial. *J Am Acad Child Adolesc Psychiatry*. 2003;42(1):22–29
35. Berard R, Fong R, Carpenter DJ, Thomason C, Wilkinson C. An international, multicenter, placebo-controlled trial of paroxetine in adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2006;16(1–2):59–75
36. Bristol-Myers Squibb. Review and evaluation of clinical data. Available at: www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM164073.pdf. Accessed August 25, 2016
37. Emslie GJ, Rush AJ, Weinberg WA, et al. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry*. 1997;54(11):1031–1037
38. Emslie GJ, Heiligenstein JH, Wagner KD, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry*. 2002;41(10):1205–1215
39. Emslie GJ, Findling RL, Rynn MA, et al. Efficacy and safety of nefazadone in the treatment of adolescents with major depressive disorder [abstract]. *J Child Adolesc Psychopharmacol*. 2002;12(4):299
40. Emslie GJ, Wagner KD, Kutcher S, et al. Paroxetine treatment in children and adolescents with major depressive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2006;45(6):709–719
41. Emslie GJ, Findling RL, Yeung PP, Kunz NR, Li Y. Venlafaxine ER for the treatment of pediatric subjects with depression: results of two placebo-controlled trials. *J Am Acad Child Adolesc Psychiatry*. 2007;46(4):479–488
42. Emslie GJ, Ventura D, Korotzer A, Tourkodimitris S. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. *J Am Acad Child Adolesc Psychiatry*. 2009;48(7):721–729
43. Emslie GJ, Prakash A, Zhang Q, Pangallo BA, Bangs ME, March JS. A double-blind efficacy and safety study of duloxetine fixed doses in children and adolescents with major depressive disorder. *J Child Adolesc Psychopharmacol*. 2014;24(4):170–179
44. Findling RL, Pagano ME, McNamara NK, et al. The short-term safety and efficacy of fluoxetine in depressed adolescents with alcohol and cannabis use disorders: a pilot randomized placebo-controlled trial. *Child Adolesc Psychiatry Ment Health*. 2009;3(1):11
45. Keller MB, Ryan ND, Strober M, et al. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2001;40(7):762–772
46. Klein RG, Mannuzza S, Koplewicz HS, et al. Adolescent depression: controlled desipramine treatment and atypical features. *Depress Anxiety*. 1998;7(1):15–31
47. GlaxoSmithKline. Paxil Japanese post marketing paediatric study in depression. (Double-blind, placebo controlled study). Identifier: NCT00812812. Available at: www.clinicaltrials.gov/ct2/show/study/NCT00812812?term=A+randomised,+double-blind,+placebo+controlled,+parallel+group,+flexible+dose+study+to+evaluate+the+efficacy+and+safety+of+PaxilÂ®+Tablets+in+children+and+adolescents+with+Major+Depressive+Disorder&rank=1. Accessed May 22, 2016
48. Wagner KD, Jonas J, Findling RL, Ventura D, Saikali K. A double-blind, randomized, placebo-controlled trial of escitalopram in the treatment of pediatric depression. *J Am Acad Child Adolesc Psychiatry*. 2006;45(3):280–288
49. Wagner KD, Robb AS, Findling RL, Jin J, Gutierrez MM, Heydorn WE.

A randomized, placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents. *Am J Psychiatry*. 2004;161(6):1079–1083

50. von Knorring AL, Olsson GI, Thomsen PH, Lemming OM, Hultén A. A randomized, double-blind, placebo-controlled study of citalopram in adolescents with major depressive disorder. *J Clin Psychopharmacol*. 2006;26(3):311–315
51. Wagner KD, Ambrosini P, Rynn M, et al; Sertraline Pediatric Depression Study Group. Efficacy of sertraline in the treatment of children and adolescents with major depressive disorder: two randomized controlled trials. *JAMA*. 2003;290(8):1033–1041
52. March J, Silva S, Petrycki S, et al; Treatment for Adolescents With Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents with Depression Study (TADS) randomized controlled trial. *JAMA*. 2004;292(7):807–820
53. Young JF, Mufson L, Gallop R. Preventing depression: a randomized trial of interpersonal psychotherapy-adolescent skills training. *Depress Anxiety*. 2010;27(5):426–433
54. Young JF, Mufson L, Davies M. Efficacy of interpersonal psychotherapy-adolescent skills training: an indicated preventive intervention for depression. *J Child Psychol Psychiatry*. 2006;47(12):1254–1262
55. Trowell J, Joffe I, Campbell J, et al. Childhood depression: a place for psychotherapy. An outcome study comparing individual psychodynamic psychotherapy and family therapy. *Eur Child Adolesc Psychiatry*. 2007;16(3):157–167
56. Tang TC, Jou SH, Ko CH, Huang SY, Yen CF. Randomized study of school-based intensive interpersonal psychotherapy for depressed adolescents with suicidal risk and parasuicide behaviors. *Psychiatry Clin Neurosci*. 2009;63(4):463–470
57. Rosselló J, Bernal G, Rivera-Medina C. Individual and group CBT and IPT for Puerto Rican adolescents with depressive symptoms. *Cultur Divers Ethnic Minor Psychol*. 2008;14(3):234–245
58. Rosselló J, Bernal G. The efficacy of cognitive-behavioral and interpersonal treatments for depression in Puerto Rican adolescents. *J Consult Clin Psychol*. 1999;67(5):734–745
59. Rohde P, Clarke GN, Mace DE, Jorgensen JS, Seeley JR. An efficacy/effectiveness study of cognitive-behavioral treatment for adolescents with comorbid major depression and conduct disorder. *J Am Acad Child Adolesc Psychiatry*. 2004;43(6):660–668
60. Mufson L, Dorta KP, Wickramaratne P, Nomura Y, Olfson M, Weissman MM. A randomized effectiveness trial of interpersonal psychotherapy for depressed adolescents. *Arch Gen Psychiatry*. 2004;61(6):577–584
61. Mufson L, Weissman MM, Moreau D, Garfinkel R. Efficacy of interpersonal psychotherapy for depressed adolescents. *Arch Gen Psychiatry*. 1999;56(6):573–579
62. Moldenhauer Z. *Adolescent Depression: A Primary Care Pilot Intervention Study* [doctoral thesis]. New York, NY: University of Rochester; 2003
63. Merry SN, Stasiak K, Shepherd M, Frampton C, Fleming T, Lucassen MF. The effectiveness of SPARX, a computerised self help intervention for adolescents seeking help for depression: randomised controlled non-inferiority trial. *BMJ*. 2012;344:e2598
64. Kerfoot M, Harrington R, Harrington V, Rogers J, Verduyn C. A step too far? Randomized trial of cognitive-behaviour therapy delivered by social workers to depressed adolescents. *Eur Child Adolesc Psychiatry*. 2004;13(2):92–99
65. Jeong YJ, Hong SC, Lee MS, Park MC, Kim YK, Suh CM. Dance movement therapy improves emotional responses and modulates neurohormones in adolescents with mild depression. *Int J Neurosci*. 2005;115(12):1711–1720
66. Israel P, Diamond GS. Feasibility of attachment based family therapy for depressed clinic-referred Norwegian adolescents. *Clin Child Psychol Psychiatry*. 2013;18(3):334–350
67. Fleming T, Dixon R, Frampton C, Merry S. A pragmatic randomized controlled trial of computerized CBT (SPARX) for symptoms of depression among adolescents excluded from mainstream education. *Behav Cogn Psychother*. 2012;40(5):529–541
68. Eskin M, Ertekin K, Demir H. Efficacy of a problem-solving therapy for depression and suicide potential in adolescents and young adults. *Cognit Ther Res*. 2008;32(2):227–245
69. Diamond GS, Wintersteen MB, Brown GK, et al. Attachment-based family therapy for adolescents with suicidal ideation: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry*. 2010;49(2):122–131
70. Diamond GS, Reis BF, Diamond GM, Siqueland L, Isaacs L. Attachment-based family therapy for depressed adolescents: a treatment development study. *J Am Acad Child Adolesc Psychiatry*. 2002;41(10):1190–1196
71. De Cuyper S, Timbremont B, Braet C, De Backer V, Wullaert T. Treating depressive symptoms in schoolchildren: a pilot study. *Eur Child Adolesc Psychiatry*. 2004;13(2):105–114
72. Clarke GN, Rohde P, Lewinsohn PM, Hops H, Seeley JR. Cognitive-behavioral treatment of adolescent depression: efficacy of acute group treatment and booster sessions. *J Am Acad Child Adolesc Psychiatry*. 1999;38(3):272–279
73. Ackerson J, Scogin F, McKendree-Smith N, Lyman RD. Cognitive bibliotherapy for mild and moderate adolescent depressive symptomatology. *J Consult Clin Psychol*. 1998;66(4):685–690
74. Brent DA, Holder D, Kolko D, et al. A clinical psychotherapy trial for adolescent depression comparing cognitive, family, and supportive therapy. *Arch Gen Psychiatry*. 1997;54(9):877–885
75. Spence SH, Sheffield JK, Donovan CL. Preventing adolescent depression: an evaluation of the problem solving for life program. *J Consult Clin Psychol*. 2003;71(1):3–13
76. McCarty CA, Violette HD, Duong MT, Cruz RA, McCauley E. A randomized trial of the positive thoughts and action program for depression among

early adolescents. *J Clin Child Adolesc Psychol*. 2013;42(4):554–563

77. Ettelson R. *The Treatment of Adolescent Depression* [doctoral thesis]. Normal, IL: Illinois State University; 2003
78. Phillips J. *An Evaluation of School-Based Cognitive-Behavioral Social Skills Training Groups With Adolescents at Risk for Depression* [doctoral thesis]. Arlington, TX: University of Texas at Arlington; 2004
79. Hoek W, Schuurmans J, Koot HM, Cuijpers P. Effects of Internet-based guided self-help problem-solving therapy for adolescents with depression and anxiety: a randomized controlled trial. *PLoS One*. 2012;7(8):e43485
80. Bolton P, Bass J, Betancourt T, et al. Interventions for depression symptoms among adolescent survivors of war and displacement in northern Uganda: a randomized controlled trial. *JAMA*. 2007;298(5):519–527
81. Clarke GN, Hornbrook M, Lynch F, et al. Group cognitive-behavioral treatment for depressed adolescent offspring of depressed parents in a health maintenance organization. *J Am Acad Child Adolesc Psychiatry*. 2002;41(3):305–313
82. Clarke GN, Hornbrook M, Lynch F, et al. A randomized trial of a group cognitive intervention for preventing depression in adolescent offspring of depressed parents. *Arch Gen Psychiatry*. 2001;58(12):1127–1134
83. RTI International. *SUDAAN [computer program]*. Version 10.0.1. SAS-Callable. Raleigh, NC: Research Triangle Institute; 2009
84. Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ. What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. *Psychiatr Serv*. 2009;60(11):1439–1445
85. Zimmerman M, Chelminski I, Posternak MA. Generalizability of antidepressant efficacy trials: differences between depressed psychiatric outpatients who would or would not qualify for an efficacy trial. *Am J Psychiatry*. 2005;162(7):1370–1372
86. Zimmerman M, Mattia JI, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry*. 2002;159(3):469–473
87. Franco S, Hoertel N, McMahon K, et al. Generalizability of pharmacologic and psychotherapy clinical trial results for posttraumatic stress disorder to community samples. *J Clin Psychiatry*. 2016;77(8):e975–e981
88. Hoertel N, de Maricourt P, Katz J, et al. Are participants in pharmacological and psychotherapy treatment trials for social anxiety disorder representative of patients in real-life settings? *J Clin Psychopharmacol*. 2014;34(6):697–703
89. Kessler RC, Avenevoli S, Ries Merikangas K. Mood disorders in children and adolescents: an epidemiologic perspective. *Biol Psychiatry*. 2001;49(12):1002–1014
90. Rao U, Chen LA. Characteristics, correlates, and outcomes of childhood and adolescent depressive disorders. *Dialogues Clin Neurosci*. 2009;11(1):45–62
91. Essau CA. Comorbidity of depressive disorders among adolescents in community and clinical settings. *Psychiatry Res*. 2008;158(1):35–42
92. Goodwin RD, Fergusson DM, Horwood LJ. Asthma and depressive and anxiety disorders among young persons in the community. *Psychol Med*. 2004;34(8):1465–1474
93. van der Lee JH, Mokkink LB, Grootenhuis MA, Heymans HS, Offringa M. Definitions and measurement of chronic health conditions in childhood: a systematic review. *JAMA*. 2007;297(24):2741–2751
94. Goldenberg IM, White K, Yonkers K, et al. The infrequency of "pure culture" diagnoses among the anxiety disorders. *J Clin Psychiatry*. 1996;57(11):528–533
95. Wehr TA, Goodwin FK. Can antidepressants cause mania and worsen the course of affective illness? *Am J Psychiatry*. 1987;144(11):1403–1411
96. Blanco C, Rafful C, Olfson M. The use of clinical trials in comparative effectiveness research on mental health. *J Clin Epidemiol*. 2013;66(suppl 8):S29–S36
97. Robinson D, Woerner M, Schooler N. Intervention research in psychosis: issues related to clinical assessment. *Schizophr Bull*. 2000;26(3):551–556
98. Olfson M, Marcus SC. Decline in placebo-controlled trial results suggests new directions for comparative effectiveness research. *Health Aff (Millwood)*. 2013;32(6):1116–1125
99. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*. 2007;297(15):1683–1696
100. March JS, Silva S, Petrycki S, et al. The Treatment for Adolescents with Depression Study (TADS): long-term effectiveness and safety outcomes. *Arch Gen Psychiatry*. 2007;64(10):1132–1143
101. Kratochvil CJ, May DE, Silva SG, et al. Treatment response in depressed adolescents with and without co-morbid attention-deficit/hyperactivity disorder in the Treatment for Adolescents with Depression Study. *J Child Adolesc Psychopharmacol*. 2009;19(5):519–527
102. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*. 2000;160(14):2101–2107
103. Richardson LP, Lozano P, Russo J, McCauley E, Bush T, Katon W. Asthma symptom burden: relationship to asthma severity and anxiety and depression symptoms. *Pediatrics*. 2006;118(3):1042–1051
104. Molina-Carballo A, Justicia-Martínez F, Moreno-Madrid F, et al. Differential responses of two related neurosteroids to methylphenidate based on ADHD subtype and the presence of depressive symptomatology. *Psychopharmacology (Berl)*. 2014;231(17):3635–3645
105. Olfson M, Blanco C, Wang S, Laje G, Correll CU. National trends in the mental health care of children, adolescents, and adults by office-based

physicians. *JAMA Psychiatry*. 2014;71(1):81–90

106. Olfson M, Blanco C, Liu SM, Wang S, Correll CU. National trends in the office-based treatment of children, adolescents, and adults with antipsychotics. *Arch Gen Psychiatry*. 2012;69(12):1247–1256

107. Cohen P, Cohen J. The clinician's illusion. *Arch Gen Psychiatry*. 1984;41(12):1178–1182

108. Flament MF, Cohen D, Choquet M, Jeammet P, Ledoux S. Phenomenology, psychosocial correlates, and treatment seeking in major depression and dysthymia of adolescence. *J Am Acad Child Adolesc Psychiatry*. 2001;40(9):1070–1078

109. Olfson M, Liu SM, Grant BF, Blanco C. Influence of comorbid mental disorders on time to seeking treatment for major depressive disorder. *Med Care*. 2012;50(3):227–232

110. Iza M, Olfson M, Vermes D, Hoffer M, Wang S, Blanco C. Probability and predictors of first treatment contact for anxiety disorders in the United States: analysis of data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Clin Psychiatry*. 2013;74(11):1093–1100

111. Hoertel N, de Maricourt P, Gorwood P. Novel routes to bipolar disorder drug discovery. *Expert Opin Drug Discov*. 2013;8(8):907–918

112. Blanco C, Iza M, Schwartz RP, Rafful C, Wang S, Olfson M. Probability and predictors of treatment-seeking for prescription opioid use disorders: a national study. *Drug Alcohol Depend*. 2013;131(1–2):143–148

113. Kirchner JE, Booth BM, Owen RR, Lancaster AE, Smith GR. Predictors of patient entry into alcohol treatment after initial diagnosis. *J Behav Health Serv Res*. 2000;27(3):339–346

114. Hoertel N, Franco S, Wall MM, et al. Mental disorders and risk of suicide attempt: a national prospective study. *Mol Psychiatry*. 2015;20(6):718–726

115. Hoertel N, McMahon K, Olfson M, et al. A dimensional liability model of age differences in mental disorder prevalence: evidence from a national sample. *J Psychiatr Res*. 2015;64:107–113

116. Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch Gen Psychiatry*. 2003;60(8):837–844

Generalizability of Clinical Trial Results for Adolescent Major Depressive Disorder

Carlos Blanco, Nicolas Hoertel, Silvia Franco, Mark Olfson, Jian-Ping He, Saioa López, Ana González-Pinto, Frédéric Limosin and Kathleen R. Merikangas

Pediatrics 2017;140;
DOI: 10.1542/peds.2016-1701 originally published online November 2, 2017;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Generalizability of Clinical Trial Results for Adolescent Major Depressive Disorder

Carlos Blanco, Nicolas Hoertel, Silvia Franco, Mark Olfson, Jian-Ping He, Saioa López, Ana González-Pinto, Frédéric Limosin and Kathleen R. Merikangas

Pediatrics 2017;140;
DOI: 10.1542/peds.2016-1701 originally published online November 2, 2017;