

A Review of the Impact of Exclusion Criteria on the Generalizability of Schizophrenia Treatment Research

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Abstract

Treatment research studies employ criteria that determine which patients are eligible to participate and which are not. When such exclusion criteria produce a treatment research sample that is a small and unrepresentative subset of all patients with a particular disease, clinicians may be hesitant to apply the research results in front-line clinical practice. Accordingly, the present paper reviews the English-language literature on exclusion criteria in schizophrenia treatment research and draws initial conclusions about their impact.

Empirically derived estimates of the rate of exclusion vary widely (31.0–98.2%), but the best available evidence suggests that about 4 in 5 patients with schizophrenia would be ineligible to enroll in a typical treatment research study. Women are particularly likely to be excluded from schizophrenia treatment research, which is problematic from both a clinical and social justice viewpoint. Excluded patients also tend to be older than eligible patients, and, though it has been examined in only a few studies, they also tend to have more severe problems at baseline and different outcomes over time than patients who are allowed to participate in research.

More limited use of exclusion criteria in schizophrenia treatment research would be beneficial in terms of increasing generalizability, but would also potentially involve costs, particularly a need for larger samples. More modest steps that would improve treatment outcome research reports include requiring a full description of the rationale for, and nature of, any exclusion criteria, and, having a designated place in the discussion section which draws attention to the proper scope of generalization.

Key Words: Generalizability, Knowledge Transfer, Schizophrenia Treatment, Research Design

Introduction

In the past forty years, research on the treatment of schizophrenia has improved dramatically in terms of more accurate diagnosis, better measurement of key variables and increased use of randomized and prospective designs (1).

These enhancements in internal validity substantially augment the ability of clinical researchers to draw accurate conclusions about which treatments are effective. That said, before applying these conclusions of treatment research, front-line clinicians understandably ask whether participants enrolled in the study resemble those they see in their clinical practice. Such questions about external validity are being increasingly raised in psychiatry (2), and in other medical specialties as well, including cardiology, oncology, nephrology and infectious disease (3–6). Exclusion criteria and their impact on the representativeness of treatment research samples are a major focus of this burgeoning literature. The present paper is, to the best of the author's knowledge, the

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first review of the evidence base on exclusion criteria in treatment research on schizophrenia and related disorders.

Exclusion criteria are rules that determine which patients may enroll in a treatment outcome study and which may not. They are more commonly employed in randomized clinical trials than in observational studies, but can be used in both types of designs (7). Researchers often use exclusion criteria in response to concerns about patient safety, study feasibility and/or interpretability of results. In other cases, the criteria have no explicit rationale, but are simply a tradition that has evolved over time within a particular research area (8).

Some schizophrenia researchers have argued in favor of reducing the extensiveness of exclusion criteria in the field's outcome research as a way to increase generalizability (8).

Exclusion criteria are by no means the only source of treatment research sample unrepresentativeness, but across prevalent chronic diseases they are the primary driver of non-enrollment in clinical research (6, 9). By definition, the more extensive a study's exclusion criteria, the less its research subjects will be representative of real-world patients. This is concerning because, across chronic disorders, some of the most widely cited treatment research studies excluded 90% or more of patients (6, 10).

Many clinicians and researchers in the schizophrenia field have questioned whether treatment research samples are similar enough to real-world patients to allow treatment research results to be safely generalized to front-line practice (11, 12), particularly in the case of vulnerable populations (e.g., the cognitively impaired, non-English speakers, ethnic minorities, the elderly [13]). This is a concern, for example, of clinical guideline development groups (1) and of reviewers of methodological standards in the field (14), and, was one of the motivations for the pragmatically designed CATIE trial (15). Some schizophrenia researchers have argued in favor of reducing the extensiveness of exclusion criteria in the field's outcome research as a way to increase generalizability (8). This proposal, which has been made in other medical fields as well, is the subject of ongoing debate, and the purpose of the paper is not to attempt to resolve it. Rather, the goals of this review are more modest: to provide a shared base of information about exclusion criteria to all participants in the ongoing dialogue about research design considerations in schizophrenia treatment research. Specifi-

cally, this review paper examines what is known about the proportion of patients with schizophrenia who are excluded from treatment research, and how they differ from those who are included.

Methods

The Cross-Disease Review of Exclusion Across Medicine (CREAM) project is a literature review of studies of exclusion criteria and their impact across a range of disciplines (e.g., oncology, cardiology, rheumatology, psychiatry). Reviewing this literature is challenging because the central concept of interest is a widely used methodological term (exclusion criteria) which appears in most reports of clinical research. In the PubMed database, a search on the term "exclusion criteria" returns over 14,000 articles and a search on the term "exclusion" returns over 60,000 articles. Adding to the difficulties, the term "exclusion criteria" has another meaning distinct from trial design, which refers to distinguishing whether particular patients should or should not be diagnosed with a particular disorder (e.g., [16]).

Therefore, a decision was made to conduct more constrained searches that would return results that could reasonably be reviewed by a single researcher (i.e., the author of this paper). Literature was identified primarily by conducting English-language searches in PubMed (date of search: July 8, 2013) on the following terms: "eligibility criteria and generalizability" (anywhere in paper), "exclusion criteria and generalizability" (anywhere in paper), "exclusion criteria" (in title of paper) and "eligibility criteria" (in title of paper). This generated 326 unique articles, all of which were read and their references to other studies of exclusion criteria obtained. These further papers were subjected to the same review process until saturation (i.e., every relevant reference in all reviewed papers had itself been reviewed). Other articles were discovered in a frankly opportunistic fashion by the author or by authors of the paper reviewed who were contacted by email. From this cross-disease pool of literature, evidence on individual diseases will be synthesized to write focused reviews for a range of diseases, including bipolar disorder, drug dependence and lung cancer. The present review focuses on those identified studies that address schizophrenia.

To be considered relevant, studies had to analyze data on 1) the prevalence and nature of exclusion criteria in a particular field, and/or 2) the impact of exclusion criteria on sample representatives or study results. In other words, a clinical trial that simply mentioned its exclusion rate in a report of its results would not be included in this review, but a substudy from the same trial that analyzed how those criteria influenced the study sample's similarity to a real-world sample of unselected patients would be included. As a final

note on definitions, some researchers describe refusal to participate in a study as an exclusion criterion, but in the CREAM study, ineligibility and refusal to participate are kept distinct because the predictors and nature of being excluded from research differ from those of being judged eligible but declining to participate (17-20).

Results

Rate of Exclusion and Baseline Differences between Excluded and Eligible Patients

A total of nine studies provided an empirical estimate of the rate of exclusion in schizophrenia treatment research. Table 1 summarizes these results, as well as those for any comparison of excluded and eligible patients that was con-

ducted in a majority of the studies.

The earliest identified study was Leff and Wing's (21) trial of medication maintenance for psychotic patients being discharged from the hospital. Of the 116 patients who formed what the authors described as the "base population" for the trial, only 35 (30.2%) were enrolled. The report is not detailed enough to determine whether this 69.8% exclusion rate was biased by the method employed to calculate it. The authors mention that an unspecified number of patients were not counted in the putatively representative base population of 116 patients against which the rate was calculated. Depending on the number and characteristics of those patients, the estimated exclusion rate could have been biased in either an upward or downward direction. The researchers did not compare excluded and eligible patients on demographic variables, but did note that the enrolled trial sample was of medium problem severity relative to the base popula-

Table 1 Summary of Findings for Variables Examined in a Majority of Studies of Schizophrenia Treatment Research Exclusion Criteria

Study-Year (N)	Exclusion Rate Estimate	Bias in Estimate of Exclusion Rate	Characteristics of Excluded Relative to Eligible		
			Female	Age	Baseline Functioning
Leff-1971 (N=116)	69.8%	Unknown	NE	NE	Medium problem severity, eligibles were drawn from both higher and lower functioning patients
Rabinowitz-2003 (N=179)	37.2–49.2%	Downward	More (35.6% versus 29.0%)	NSD	NSD
Boter-2010 (N=493)	31.0%	Downward	Less (25% versus 47%)	Younger (25.1 years versus 26.5)	More depression
Zarin-2005 (N=81)	38.0%	Downward	More (64.2% versus 24.5%)	Older (54.0 years versus 44.4)	Poorer global functioning, more medical comorbidities
Robinson-1996 (N=6,012)	78.0%	None	More (44% versus 39%)	Older (37% versus 19% over age 37)	NE
Barnett-2011 (N=8,039)	76.7%	Downward	NSD	Older (57.2 years versus 51.0)	Less depression, substance use disorder and medical comorbidities
Hofer-2000 (N=200)	81.6–86.5%	Upward	NSD	Older (35.8 years versus 29.7)	Longer time since onset, more psychotic episodes
Woods-2000 (N=1,655)	92.8%	Upward	More (47% versus 33%)	Older (45.3 years versus 39.6)	NSD
Khan-2005 (N=N/A)	98.2%	Upward	NE	NE	NE

NE=not examined; NSD=no significant differences.

tion, which included both higher severity and lower severity patients.

Rabinowitz and colleagues (22) used a similar design to compare subjects in first-episode psychosis drug trials to 191 “representative patients” in the Suffolk County Mental Health Project who were diagnosed with schizophrenia, schizoaffective disorder or schizophreniform disorder. This “representative” base sample is not completely representative of all people hospitalized for these disorders because the Suffolk County study excluded patients who were younger than 15 or older than 60, lived out of the county, did not speak English, had moderate or severe mental retardation or had been hospitalized at some point more than six months prior to their current admission (23).

The exclusion criteria evaluated were from a multi-site clinical trial of haloperidol versus risperidone. Of the 191 Suffolk County patients, 71 (37.2%) would have been ineligible under the trial’s exclusion criteria. The most common reasons for ineligibility under a single-exclusion criterion (some patients were excluded by several) were current antidepressant medication ($n=26$), alcohol/drug abuse ($n=17$), being too young or too old ($n=11$), and having a suicide attempt history ($n=9$).

As mentioned, the 37.2% figure is a downwardly biased estimate because a number of patients who would probably not have qualified for the clinical trial were excluded from the Suffolk County study that provided the “representative” sample. A different report from the Suffolk County study (23) estimated its exclusion rate at 19.1%, so one could extrapolate that the proportion of all psychotically ill individuals admitted to hospitals who would have been excluded from the multi-site clinical trial was $19.1\% + (37.2\% \times 80.9\%) = 49.2\%$.

The researchers then compared the 529 clinical trial participants to the 177 Suffolk County Mental Health Project patients who were in the trial’s age range of 16–45 (irrespective of whether they would have been excluded under the trial’s other exclusion criteria). Age, age of onset and average premorbid functioning were similar across the two samples. There was a trend for the trial sample to have a higher proportion of males than did the more representative sample, indicating that female patients were disproportionately excluded under the trial’s criteria.

Rabinowitz and colleagues’ study, like most clinical trials of schizophrenia treatment, excluded patients who were suicidal or had substance use disorders (22). The EUFEST trial of treatment for first-episode schizophrenia was an exception to this rule, and its research team exploited this fact to compare EUFEST participants who would have been excluded under suicidal or substance use disorder criteria with

those who would have been eligible for research participation (24). About one-third (31.0%) of participants were suicidal or had a current/past year substance use disorder and, therefore, would have been excluded from typical schizophrenia treatment research. This 31% should be considered a downwardly biased estimate of the degree of exclusion in schizophrenia treatment research more generally, because suicidality and substance use disorder are only two of the exclusion criteria that are commonly used in trials of antipsychotic medication (14). Also, the “representative” sample to which the excluded patients were compared was the subset of real-world patients who became enrolled in a clinical trial. Particularly, the authors noted that the prevalence of substance use disorder and suicidality in the EUFEST sample was less than a third of what would be typical outside of a clinical trial environment.

Excluded patients in Boter and colleagues’ EUFEST study (24) were less likely to be female (25% versus 47%) and were slightly younger (25.1 years versus 26.5 years) than included patients. Clinically, excluded patients had higher rates of depression at baseline, but were otherwise similar to included patients.

Zarin and colleagues (25) used a sample of 81 patients with schizophrenia treated in the American Psychiatric Association practice research network to judge the representativeness of the participants in Marder and Meibach’s (26) influential randomized clinical trial of risperidone. The two exclusion criteria used in the trial which Zarin et al. examined were being a woman of childbearing age and having a serious comorbid medical diagnosis. A total of 38.0% of patients in the practice research network were excluded under these criteria. Because other exclusion criteria in the risperidone trial were not evaluated (e.g., age under 18 and older than 65, history of drug/alcohol abuse, a comorbid psychiatric or neurological disorder, see Chouinard et al., [27]), the 38.0% should be considered downwardly biased relative to the proportion of real-world patients who would have been excluded from the trial. (Note: Zarin and colleagues presumably relied on the briefer paper from the U.S. arm of the risperidone study, which only included some of the exclusion criteria employed. A longer report from the Canadian arm of the study provides a more extensive list. Dr. Marder confirmed [personal communication, October 28, 2013] that the Canadian arm had the same protocol as the U.S. arm.)

Zarin and colleagues found that excluded patients were significantly more likely to be female (64.2%) than were eligible patients (24.5%), and were also older (54.0 years versus 44.4 years for eligible patients). In terms of functioning, excluded patients had significantly lower Global

Assessment of Functioning (GAF) scores (40.2 versus 46.2 for eligible patients) and more medical comorbidities.

Like Zarin et al.'s study, Robinson and colleagues' (28) evaluation of the impact of exclusion criteria within the Treatment Strategies in Schizophrenia study had a representative sample of patients against which to judge the generalizability of the research sample: all inpatients admitted with a diagnosis of schizophreniform, schizophrenia or schizoaffective disorder. Of 6,012 diagnostically appropriate patients screened, 78.0% were excluded by the criteria employed in a multi-center trial of a combined pharmacotherapy/family education intervention (28). Although not the primary focus of this review, it is of interest that the researchers also reported that of the 1,320 eligible patients, only 528 consented to enroll (9% of the screened sample), a vivid illustration of the difficulties of accruing large samples for tightly controlled trials.

The most common reasons for exclusion were lack of weekly family contact (42%), being transient/likely to leave the area (11%), and substance dependence (7%). As with most other studies in this area, women and older patients were particularly likely to be excluded.

The only other identified study that had an extremely large sample was Barnett and colleagues' (29) analysis of the representativeness of participants in a Veterans Health Administration multi-site trial of injectable risperidone. The central comparison of interest in this study was between 7,670 veterans with schizophrenia who were excluded by the study's requirement for a history of psychiatric hospitalization in the past 24 months, and the 369 enrolled participants who had such a psychiatric hospitalization history. The study's estimated exclusion rate of 76.7% is downwardly biased because the multi-site clinical trial did include some other exclusion criteria (e.g., serious medical conditions, unstable living arrangements) that were not evaluated. This downward bias is likely small since the primary exclusion criteria—in contrast to most studies—was intended to exclude individuals with *less* severe problems (i.e., it was a population with a low rate of serious medical comorbidities and unstable living arrangements). (Note: personal communication with Dr. Rosenheck, March 13, 2014.)

Enrolled patients did not differ from ineligible patients on gender, although this would have been unlikely in any event given that the overall sample was 93.5% male. Ineligible patients were significantly older (57.2 years) than enrolled patients (51.0 years). As intended by the researchers, excluded patients had less severe problems than included patients. Specifically, excluded patients were less likely to have a comorbid substance use disorder (13.9% versus 46.3%), comorbid depression (19.3% versus 38.8%), and medical comorbidities (73.9% versus 78.7%).

Hofer and colleagues (30) reported that of 200 consecutive inpatients with a diagnosis of schizophreniform or schizophrenic disorder, only 27 (13.5%) were enrolled in a clinical trial of antipsychotic medication. This 86.5% "exclusion rate" should be regarded as upwardly biased because it includes 26 patients who refused to provide informed consent to participate. At least some of these patients would presumably have met eligibility criteria, but the report does not break down the data in sufficient detail to determine how many. Further, the report mentions that 27 patients were not enrolled because "no suitable study was available," but does not specify if this means no studies at all were available or only studies from which these patients were excluded were available. If one leaves out of the exclusion rate calculation, the 26 patients who refused and the 27 patients who were described as having no appropriate study available, the exclusion rate for this study would drop to 81.6% (120 patients excluded of the 147 for which the report provides sufficient detail to be certain).

The representative patient sample did not differ on gender from the research sample. However, as in other studies discussed above, excluded patients tended to be older than eligible patients. Excluded patients also had a longer time since illness onset and a higher number of prior psychotic episodes than eligible patients.

Within a sample of individuals with a schizophrenia or schizoaffective disorder seen at a community mental health clinic, Woods et al. (31) compared the 119 who had participated in one or more medication clinical trials with the 1,536 who did not. The medication trials included those focused on patients with psychotic disorders only, as well as those focused on patients with co-occurring substance use disorders. The non-enrollment rate of 92.8% is an upwardly biased estimate of the exclusion rate as the researchers did not have the data to distinguish excluded patients from those who were eligible but refused to participate.

Because the main analysis did not differentiate nonparticipants who were and were not dual-diagnosed, discussion here will focus on differences between nonparticipants and participants in standard trials. Excluded participants were more likely to be female (47% versus 33% for standard trial) and were also older (45.3 years of age versus 39.6 years for standard trial participants). There were no racial differences between nonparticipants and included patients. GAF scores did not differ between groups either currently and over the past year.

Finally, in a simulation study, Khan and colleagues (32) examined the common exclusion criteria for antipsychotic medication trials used at their research institute and then employed epidemiologic data and chart review to estimate

impact on enrollment. The criterion that had the largest impact was being on a specific mono-drug therapy, which excluded 92% of outpatients with schizophrenia. Other influential exclusions were that subjects be male (50% of patients excluded), not have alcohol/drug use disorders (35%), be within 20% of ideal weight (30%) and not have hepatitis B/C or HIV/AIDS (3.5%). Taking a broad range of possible exclusion criteria into account, the research team concluded that of a sample of 36,000 people with schizophrenia, only 632 would meet eligibility criteria for an antipsychotic medication trial. This exclusion rate of 98.2% is an upwardly biased estimate, in that most treatment research outcome studies in the field use fewer criteria than those tested by Khan et al. (see [14] for a review). Khan and colleagues did not have the data to directly compare excluded and eligible patients, but summarized their simulation results by noting that “the results emphasize the rarefied nature of patient-volunteers who enter a clinical trial.”

Outcome Differences between Excluded and Eligible Patients

Only three studies examined whether excluded patients responded to treatment differently than eligible patients. Leff and Wing (21) were able to gather one-year follow-up information on a remarkable 95% of the excluded patients. Relative to the enrolled patients—who had a relapse rate of 53.3%—the excluded patients included subgroups with significantly better (e.g., 27.3% relapse rate among those excluded because their prognosis was unusually positive) and significantly worse outcomes (e.g., 87.5% among those excluded for not showing a response to medication in the hospital). In contrast, Boter and colleagues (24), using the EUFEST data, found that the differences were all in one direction: excluded patients were more likely to be re-hospitalized during the follow-up period than were eligible patients.

Finally, though they had no direct data, Robinson and colleagues (28) modeled the potential impact of exclusion criteria on study outcome. Based on the fact that female patients often have different outcomes than males, the researchers calculated that a family contact exclusion criterion—which reduces the number of women enrollees—could plausibly change a study’s positive outcome rate by as much as 50% (i.e., raise it from 43% to 65%). This projection is based only on their own study, but since most of the studies just reviewed found sex differences in rate of exclusion, it may have much broader applicability.

Discussion

Although there has been a recent uptick in concern about whether exclusion criteria produce treatment research

samples that are unlike patients seen in front-line practice, the question is clearly not a new one: the first study of the question identified here was published over forty years ago (21). Based on the studies conducted over that time, it is possible to provide a tentative global estimate of the exclusion rate in schizophrenia treatment research. The estimate must remain tentative for several reasons. First, the number of studies of the question of interest is not large. Second, definitions of schizophrenia have changed over the forty years of studies reviewed. Third, this literature review was the work of a single individual. A grant-supported systematic literature review with a large number of reviewers involved may well have found more articles than did the present author, would have been able to conduct inter-judge reliability checks on whether individual articles should have been included, would have likely been able to evaluate non-English language literature, and would have been able to conduct a formal quantitative synthesis as is recommended in PRISMA guidelines (33).

To avoid false precision, a rule of thumb of “about 4 in 5” excluded might constitute the best summary of current knowledge.

Determining the exclusion rate must be done in the context of the varying methods employed to estimate it. The one study which appeared completely unbiased in method was Robinson and colleagues (28), which estimated the exclusion rate at 78%. The study with the next least likely bias (29)—moderately downward—was similar: 76.7%. Importantly, the sample sizes of these two studies were each as large as the other seven studies combined, making their estimate of exclusion rate more likely to represent the population value than the parallel estimates of the smaller sample studies reviewed here. Studies that adopted methods that would tend to underestimate the exclusion rate (e.g., Rabinowitz [22], Boter [24] and Zarin [25])—by only examining a few criteria or by using a pre-selected sample to judge generalizability—generate rates below the Barnett (29) and Robinson (28) estimates. Studies with methods that would tend to bias the estimate rate of exclusion upward (e.g., Hofer [30], Woods [31] and Khan [32] for example) by not clearly distinguishing ineligible patients from refusers, produce estimates that are higher than the Barnett (29) and Robinson (28) estimates. Thus, it seems reasonable to take these two large studies’ results as the best current estimate of the exclusion rate in schizophrenia treatment research. To avoid false precision, a rule of thumb of “about 4 in 5” excluded might constitute the best summary of current knowledge.

How this typical rate of exclusion compares to that in other treatment research areas is something that the CREAM study intends to systematically examine, as it conducts parallel reviews for other diseases. To cite a few individual examples: Zimmerman and colleagues (34) found that 91.6% of typical depressed outpatients would be excluded under the most common depression treatment enrollment criteria; Hoertel and colleagues (2) found that 81.8% of individuals seeking treatment for generalized anxiety disorder would be excluded from typical clinical trials; and, Hlatky and colleagues (5) reported that between 87–96% of patients with heart disease would have been excluded from the most influential clinical trials of coronary artery bypass surgery. Thus, the challenge of high-exclusion rates does not appear unique to schizophrenia treatment research.

Most importantly, of the seven studies examining gender differences, four found that women are disproportionately excluded from treatment research by exclusion criteria.

Only a few variables have been researched sufficiently to begin to describe how patients excluded from schizophrenia treatment research differ from those who are judged eligible. Most importantly, of the seven studies examining gender differences, four found that women are disproportionately excluded from treatment research by exclusion criteria. This is of concern for several reasons. First, the NIH guidelines (35) require that women should be represented in research samples proportionate to their representation in the population that has the disorder under study. Second, because patient sex often is a significant predictor of outcomes for treatments for schizophrenia, artificial sex ratios in research samples will distort estimates of how well treatments actually work in the real world.

The other demographic pattern in the results was that relatively older patients were more likely to be excluded than younger patients. This finding was present in five of seven studies which examined it, was absent in another, and was reversed (albeit a potentially spurious finding borne of multiple tests) in another. This finding may be logically linked to four of the seven studies of disease severity (e.g., lifetime number of hospitalizations, time since onset), finding that patients with more severe problems at baseline are particularly likely to be excluded from research. This may reflect a trend for patients with longer illness histories (who would also tend to be older) to be disproportionately excluded rela-

tive to patients who are in the early stages of their disease. The effect of this exclusion is unknown, but conceivably it might produce more optimistic assessments of treatment effects than are seen in settings where most patients have long illness histories (see also [36]).

The other demographic pattern in the results was that relatively older patients were more likely to be excluded than younger patients.

Only two studies provided direct outcome data and one had modeled data, but all three converged on the conclusion that excluded patients have different outcomes than eligible patients. This suggests that clinicians cannot assume that a treatment's results in a research sample will necessarily be replicated on the front-lines of healthcare. This is a key reason why post-approval monitoring and effectiveness oriented health services research (37) are so important, even for "proven" treatments.

The high rate of exclusion discovered by researchers and the differences between excluded and included patients raises the question of how to make treatment research samples more like those encountered in everyday practice. Few researchers would argue with Robinson, Warner and Schooler's (8) suggestion that researchers be wary of exclusion criteria that have simply been copied and pasted from protocol to protocol over time. Like any other methodological decisions, exclusion criteria should be based on an explicit rationale that carefully weighs costs and benefits (38).

Some schizophrenia researchers and indeed researchers in other fields make the case that a general relaxation of exclusion criteria in treatment research would benefit science and clinical practice (4, 8, 38). This is more than the endorsement of the occasional large, simple trial (though those are important to conduct [14, 39, 40]), as it implies a change in how clinical trials in general are routinely designed. Given that about 80% of patients with schizophrenia cannot enroll in the treatment research that is supposed to guide their care, a case for this proposal can be made on the grounds of clinical relevance as well as professional ethics that treatment research more generally should include a greater proportion of patients. To put it bluntly, the wisdom of excluding from schizophrenia treatment research patients who have substance use disorders or suicidal impulses may be more evident to the researcher than it is to the clinician charged with taking care of the very large number of patients with schizophrenia who suffer from one or both of these comorbid problems.

That said, relaxing exclusion criteria can result in a loss of statistical power if the newly included patients respond to treatment differently than the currently included (41). The “sweet spot” would be loosened eligibility criteria that save enough resources through reducing the needed recruiting period (42) to allow a larger number of participants, thereby providing compensatory statistical power for any increase in sample heterogeneity. Minimizing eligibility criteria may also help address the common problem of trials being underpowered because they did not meet their recruitment target (43).

This suggests that clinicians cannot assume that a treatment's results in a research sample will necessarily be replicated on the front-lines of healthcare. This is a key reason why post-approval monitoring and effectiveness-oriented health services research (37) are so important, even for “proven” treatments.

Regardless of whether a broad-based move to more representative samples is embraced by treatment researchers, some more modest steps seem likely to be widely agreeable. First, as specified in the CONSORT criteria (44), all treatment research studies should fully report their exclusion criteria, the proportion of patients excluded by each criterion and in total, and any analyses of how excluded patients differ from study participants. There has been improvement on this front in recent years, but a large proportion of even highly cited trials still fails to provide this information (7, 9, 10, 45).

Further, following Rothwell (46), schizophrenia treatment research reports could include a “To whom do these results apply?” section. Exclusion criteria are often forgotten by readers (and perhaps authors as well) when the time comes to draw conclusions in a scientific paper. It could, therefore, be beneficial for journal articles to close with a reminder that narrowness in design places limits on the breadth of a study's conclusions.

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