Intention-to-Treat Analyses and Missing Data Approaches in Pharmacotherapy Trials for Alcohol Use Disorders

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Intention-to-Treat Analyses and Missing Data Approaches in Pharmacotherapy Trials for Alcohol Use Disorders

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Abstract

Objective: Intention-to-treat (ITT) is an analytic strategy for reducing potential bias in treatment effects arising from missing data in randomized controlled trials (RCT). Currently, no universally accepted definition of ITT exists, although many consider it to require either no attrition or some imputation procedure to account for missing outcome data in analyses. Using the reports of a large pool of randomized controlled trials, we examined discrepancies between the types of analyses that alcohol pharmacotherapy researchers stated they used versus those they actually used. We also examined the linkage between analytic strategy (i.e., ITT or not) and how missing data on outcomes were handled (if at all), and whether data analytic and missing data strategies have changed over time.

Method: Descriptive statistics were generated for reported and actual data analytic strategy and for missing data strategy for 165 RCTs of pharmacotherapy for alcohol use disorders (AUDs). In addition, generalized linear models determined changes over time in the use of ITT analyses and missing data strategies.

Results: Of the 165 studies, 74 reported using an ITT strategy. However, based on their reports, less than 40% of the studies actually conducted ITT according to the rigorous definition above. The most common method utilized for studies reporting ITT, but not actually using one, involved analyses of data for participants who completed what was deemed a sufficient dose of treatment. Whereas no change in the use of ITT analyses over time was found, censored (last follow-up completed) and imputed missing data strategies have increased over time, while analyses of data only for the sample actually followed have decreased over time.

Conclusion: Discrepancies in reporting versus actually conducting ITT analyses were found in this body of RCTs. Lack of clarity regarding the missing data strategy used was common.
Consensus on a definition of ITT is important for adequate understanding of research findings. Clearer reporting standards for analyses and the handling of missing data in pharmacotherapy trials and other intervention studies are needed.
In pharmacotherapy trials, participants typically are randomly assigned to a pharmacotherapy or a placebo (control) condition. With a sufficient sample size, randomization usually produces separate groups without systematic differences by equalizing factors within groups that may be associated with outcome (e.g., motivation, age, gender). Under ideal circumstances, the randomization process allows valid causal inferences to be made about the impact of the pharmacotherapy compared to the control condition. That is, one can be highly confident that any post-treatment differences in outcome are attributable to the impact of the medication itself and not to pre-existing differences between the characteristics of the pharmacotherapy and placebo samples. However, when the randomization process is disrupted, either through treatment dropout and/or missing data on outcomes, or when the original sample as randomized is not the same sample analyzed (analyzed \( N < \) randomized \( N \)), bias may be introduced that compromises the internal validity of results. 1–4

The intention-to-treat (ITT) analytic strategy is one solution for eliminating or reducing bias in treatment effects arising from missing outcome data in randomized controlled trials (RCTs). 1,2 Although no universally accepted definition of ITT currently exists, the procedure nevertheless is endorsed in the Consolidated Standards for Reporting Trials (CONSORT). 5–7 One particularly succinct definition of a "true ITT" analysis is "once randomized, always analyzed" (Schulz and Grimes, 2002, p. 781). Under this definition, ITT involves analysis of all trial participants who were randomized, regardless of adherence to treatment protocol (e.g., dropout/withdrawal or protocol deviations). In other words, defined this way, ITT requires either no attrition or some imputation procedure to account for any missing data.

ITT has several strengths, including (1) helping to preserve the integrity of the randomization process (i.e., groups are expected to be similar except for random variation and
receipt of treatment/control condition) and (2) providing a more realistic estimate of average treatment effects in the "real-world" as it is the norm for some patients to dropout or not adhere to treatment. ¹ Both points above address the issue of patient dropout, as analyses on only adherent patients likely would lead to inflated estimates of treatment effects. Research has shown that adherent patients generally do better than non-adherent patients, regardless of treatment.¹⁰ ¹¹ The more realistic estimates of treatment effects under conditions of routine care that are derived from ITT analyses have particular relevance for policy makers and those interested in hypotheses of pragmatic ("real world") importance.

A variant of the ITT approach, what it termed a “modified ITT” analysis, ⁸ maintains the conditions to which people were randomly assigned and attempts to follow-up all participants, regardless of their participation in the intervention. However, only those successfully followed are included in the analyses. With this modified approach, however, the balance in pre-existing characteristics across conditions sought through random assignment is less likely to hold.

An alternative to ITT analysis, the per protocol analytic procedure (i.e., analyses based on only “adherent” participants in randomized samples), has strengths as well and is of particular importance for hypotheses of an explanatory nature.¹² The per protocol approach can range from analyses in which only those research participants who began treatment are included, to those in which only participants who received what was deemed a “sufficient dose” of treatment are used, to those in which only participants who fully completed treatment are included (also referred to as a ‘complete cases’ approach). ² Advocates of per protocol approach assert that the analysis tests the true efficacy of the intervention when used as directed (i.e., efficacy among those who are adherent and able to tolerate the treatment).
Because both ITT and per protocol approaches to RCT analyses have their strengths, a possible strategy is to conduct an ITT analysis, with a per protocol sensitivity analysis to “bracket” likely effects under different conditions. Nevertheless, ITT analyses are considered the "gold standard" and researchers frequently report the use of this procedure in published literature, even in the absence of a consensual definition. Discrepancies can arise, however, between the type of analyses researchers state in research reports that they conducted and what they actually did with respect to use of a “true” ITT analysis or some other procedure based on less than the full randomized sample. For example, in clinical trials in the nursing field, Polit and Gillespie found that for 10.5% of studies, researchers who stated they had used an ITT approach had actually conducted per protocol analyses.

In this review, we examined discrepancies between the types of analyses that researchers stated they used and those they actually used in reports of a large pool of randomized controlled trials of pharmacotherapy for alcohol use disorders published between 1970 to 2009. We also examined the use of different missing data strategies in studies in which true and modified ITT analyses were and were not conducted. Finally, we examined whether the use of different data analytic approaches and certain types of missing data approaches (e.g., multiple imputation) has increased over time while the use of others has decreased.

**Methods**

**Literature Search**

As part of a larger project examining the efficacy of pharmacotherapies for alcohol use disorders and alcohol misuse, we identified relevant randomized controlled trials via several searches of PubMed and PsycINFO conducted at different points over the past decade. Study inclusion criteria were (a) a focus on treating alcohol misuse or an alcohol use disorder; (b) participants 18 years of age or older; (c) publication between 1970 and 2009; (d) a report in the
English language; and (e) random assignment of at least five participants each to medication and placebo groups.

Searches were intermittent due to sporadic availability of funds and resources. For example, in one search we used search terms for various medications (e.g., “naltrexone”), terms for alcohol problems and use disorders and alcohol misuse (e.g., “alcohol*,” “problem drinking”) and terms for randomized controlled trials (e.g., “randomized controlled,” “clinical trial”). This search yielded 1,602 potential research reports. Based on examination of abstracts and full text versions of these reports, 1,184 were identified as not relevant (e.g., qualitative studies, reviews). Of the remaining articles, 215 were rejected based on not meeting our eligibility criteria (e.g., open-label trial), 138 articles met the inclusion criteria, but 65 were additional publications for studies already in the dataset (e.g., reporting secondary analyses). In addition to the database searches, we pursued the reference sections from the reports of the included studies and from previously published reviews of this literature. For the present analysis, a total of 165 studies met our inclusion criteria.

Variables

Descriptive and inferential statistics were generated for two categorical variables: (1) sample analyzed and (2) missing data strategy. The categories of the “sample analyzed” variable were:

1. Full random sample - analyses involved the total randomized N’s (with or without imputation of missing data)
2. Full random sample (likely) - analyses appeared to use the full randomized sample, but N’s were not reported
(3) Random sample followed-up - attempted to follow-up all randomized participants regardless of amount of medication/treatment completed and conducted analyses on this sample

(4) Sufficient dose - analyses were conducted for only those participants who completed a specified amount of treatment or who received at least a minimum dose of treatment

(5) Completer sample - analyses conducted for only those patients who completed the medication/treatment phase

(6) False inclusion - after randomization, participants were found to not meet inclusion criteria and were subsequently removed from the analyses

(7) Other - reported N’s or degrees of freedom that were less than what would be expected for the randomized N, but no explanation of the participants included or excluded from the analysis was provided

(8) Unclear – insufficient information was provided to determine the sample analyzed.

Only analyses conducted on the Full Random Sample or Full Random Sample (likely) categories were deemed to be “true” ITT analyses, whereas the others were considered something other than ITT analyses.

For those studies in which ITT analyses were actually conducted (i.e., “true” ITT with no missing outcome data due to 100% reassessment rate or imputing missing data), the categories for the “missing data strategy” variable were as follows:

(1) No dropout – no dropout from treatment and 100% reassessed

(2) All followed - there were drop-outs from treatment, but all participants, including treatment dropouts, were reassessed
(3) Statistical imputation - used a statistical analysis that imputed missing data, e.g.,
mixed-model imputation

(4) Failure assumed for missing data (missing = failure) - assumed that missing data
reflected poor outcome, e.g., relapse

(5) Baseline assigned - a participant’s baseline score was assigned if outcome data were
missing

(6) LOCF - used the imputation strategy of Last Observation Carried Forward

(7) Censored – last assessment point was used in survival analyses

(8) Mean - used the mean of the sample followed for missing data

(9) Other – used some other imputation of missing data strategy

(10) Sample followed - conducted analyses with data for the sample of participants that
the researchers were able to follow/reassess

(11) Unclear - no or unclear information provided.

Statistical Analyses

Descriptive statistics were generated for data analytic strategies and missing data
strategies used in the 165 RCTs of pharmacotherapies for AUD and alcohol misuse. Generalized
linear model analyses were conducted to determine changes in both data analytic and missing
data strategy over time. In those analyses, the response variables, data analytic strategy and
missing data strategy, were coded as binary (0='No', 1='Yes'), with year of publication as
predictor of a 'Yes' response.

Results

As noted in Table 1, a substantial discrepancy was evident between reporting an ITT
strategy versus actually conducting a “true” ITT analysis (i.e., reporting an ITT strategy when
something other than ITT was conducted). Of the 165 studies included in this review, 74 reported using an ITT strategy. However, less than half of those studies conducted a true ITT analysis ($K=29; 39\%$) according to information in study reports. Interestingly, $35\% (K=32)$ of the 91 studies whose reports made no claim of using an ITT strategy, in fact, did perform true ITT analyses.
Table 1.

<table>
<thead>
<tr>
<th>Reported Using ITT</th>
<th>Conducted True ITT</th>
<th>Sample Analyzed</th>
<th>Number of IIT and/or Non-ITT Approaches Used</th>
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<tr>
<td></td>
<td></td>
<td>Full Random Sample</td>
<td>Full Random Sample (likely)</td>
</tr>
<tr>
<td>No</td>
<td>32 (35%)</td>
<td>28 (4%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Yes (K=74)</td>
<td>29 (39%)</td>
<td>21 (9%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Total (K=165)</td>
<td>61 (37%)</td>
<td>49 (23%)</td>
<td>13 (6%)</td>
</tr>
</tbody>
</table>

Note: aITT=Full Random Sample or Full Random Sample (likely) categories; K=study, column description: (1) Full random sample (analyses involved the total randomized N’s), (2) Full random sample (likely) (appears to be using the full randomized sample, but N’s are not reported with analyses), (3) Random sample followed-up (attempted to follow-up all randomized participants regardless of amount of medication/treatment completed, and conducted analyses on this sample), (4) Sufficient dose (analyses conducted on only those participants who received a minimum amount of medication/treatment), (5) Completer sample (analyses conducted on only those patients who completed the medication/treatment phase), (6) False inclusion (after randomization, participant is found to not meet inclusion criteria and is subsequently removed from the analyses), (7) Other (analyses report N’s or degrees of freedom that are less than what would be expected for the randomized N, but no explanation on the participants included or excluded from the analysis is provided), and (8) Unclear (insufficient information to determine the sample analyzed). Only categories (1) Full random sample and (2) Full random sample (likely) are considered a “true” ITT strategy, whereas the others are considered something other than ITT.
Regarding the specific data analytic strategy used, the values in each row of Table 1 do not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming failure for dichotomous outcomes AND also used a complete cases approach for continuous outcomes). In such instances, we coded "Reported Using ITT" as "Yes" if the study mentioned using an ITT strategy and coded it as "No" otherwise (i.e., no mention of using an ITT strategy).

The most common approach utilized in studies reporting the use of an ITT strategy, other than use of a true ITT ($K=29; 39\%$), involved analyses of data for participants who completed a “sufficient dose” of the medication/treatment ($K=40; 39\%$). All other strategies were utilized <10% of the time. The most common analytic method used in studies not mentioning an ITT strategy was actually a true ITT analysis ($K=32; 29\%$), followed by analyses of data from completer samples ($K=31; 28\%$), analyses for participants who completed a “sufficient dose” of medication/treatment ($K=19; 17\%$), and indeterminable strategies (i.e., Unclear; $K=16; 14\%$).

Table 2 reports the descriptive information on the missing data strategies employed in the studies using and not using a true ITT approach. Similar to Table 1, the values in each row of Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due to 42 studies utilizing multiple missing data strategies. The most common missing data strategy utilized in studies employing an ITT approach was either unclear ($K=24; 23\%$) or involved censoring data at the end of FU procedure in survival analyses ($K=23; 22\%$). A study could be categorized as employing an ITT strategy, but having an unclear missing data strategy if, for example, the study reported the full randomized $N$s from analyses, but it was unclear what particular missing data strategy was utilized. The next most frequently used strategies were
assuming missing equals relapse or some other poor outcome ("Failure"; $K=14$; 13%) and using a statistical imputation strategy ($K=14$; 13%), such as a mixed effects model. All other missing data strategies were utilized ≤10% of the time, except the last observation carried forward (LOCF) procedure that was used in ($K=12$) 11% of the studies.
Table 2.

<table>
<thead>
<tr>
<th>Conducted True ITT</th>
<th>Missing Data Strategy</th>
<th>Mean Substituted</th>
<th>Other</th>
<th>Sample FU</th>
<th>Unclear</th>
<th>Total Number of ITT and/or Non-ITT Approaches Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Tx or FU Dropout</td>
<td>All FU (some tx dropout)</td>
<td>Imputed Failure</td>
<td>Baseline Assigned</td>
<td>LOCF (end of FU)</td>
<td>Censored Survival Analysis</td>
<td></td>
</tr>
<tr>
<td>No (K=104)</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>23</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td>Yes (K=61)</td>
<td>1</td>
<td>2</td>
<td>14</td>
<td>14</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Total (K=165)</td>
<td>1 (&gt;1%)</td>
<td>2 (&gt;1%)</td>
<td>20 (07%)</td>
<td>37 (16%)</td>
<td>2 (&gt;1%)</td>
<td>34 (13%)</td>
</tr>
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</table>

Note. Column description: (1) No dropout, (2) Followed-up (some dropout) (there were drop-outs from treatment, but all participants, including dropouts were followed-up), (3) Imputed (used a statistical analysis that imputed missing data, e.g., mixed-model), (4) Failure (assumed that missing data = failure, e.g., relapse), (5) Baseline assigned (assigned a person’s baseline score if the outcome score was missing), (6) LOCF (used an imputation strategy of Last Observation Carried Forward), (7) Censored (end of FU) (data presented in a survival analysis), (8) Mean (used the mean for each person across available assessments/timepoints), (9) Other (other imputation strategy), (10) Sample FU (conducted analyses on the sample of participants that the researchers was able to follow-up), (11) Unclear (no information provided/unclear). It was unclear whether an ITT analysis was conducted or not for 15 analyses.
The most common missing data method utilized in studies not conducting a true ITT analysis was analyzing the sample followed-up (K=38; 27%), followed by censoring at the end of FU procedure (K=25; 18%), assuming failure (“Failure”; K=23; 17%), last observation carried forward (K=23; 16%) and an unclear strategy (K=17; 12%). All other missing data strategies were used ≤10% of the time. A study could be categorized as not employing an ITT strategy, but still using a missing data strategy of assuming failure or last observation carried forward if, for example, the study assumed failure for missing participants, but something less than the full randomized Ns were reported for analyses. Tables 3 and 4 display changes in ITT analyses and missing data strategies over time. No statistically significant changes were found in use of true ITT analyses over time (Table 3). However, several statistically significant relationships between missing data strategy and time emerged, as displayed in Table 4. Specifically, censored at end of FU (for survival analyses), last observation carried forward (LOCF), and using a statistical analysis to impute missing data (Imputed, e.g., mixed-model) have become more common over time, whereas analyses conducted on the sample of participants that the researchers were able to follow-up (Sample FU) has become less common.
### Table 3. Change in true ITT analyses over time

<table>
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<th>Estimate</th>
<th>SE</th>
<th>t-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-1.44</td>
<td>0.62</td>
<td>-2.33</td>
</tr>
<tr>
<td>Year</td>
<td>0.03</td>
<td>0.02</td>
<td>1.54</td>
</tr>
</tbody>
</table>

Note: generalized linear model with binary outcome
(ITT analyses conducted=1 or not=0)

### Table 4. Change in missing data strategy over time

<table>
<thead>
<tr>
<th>Estimate</th>
<th>SE</th>
<th>z-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fail</td>
<td>0.03</td>
<td>0.02</td>
<td>1.38</td>
</tr>
<tr>
<td>All FU</td>
<td>-0.10</td>
<td>0.09</td>
<td>-1.18</td>
</tr>
<tr>
<td>All FU (some dropout)</td>
<td>-0.09</td>
<td>0.06</td>
<td>-1.43</td>
</tr>
<tr>
<td>Baseline Assigned</td>
<td>0.47</td>
<td>0.36</td>
<td>1.31</td>
</tr>
<tr>
<td>Censored (end of FU)</td>
<td>0.09</td>
<td>0.03</td>
<td>3.19</td>
</tr>
<tr>
<td>LOCF</td>
<td>0.06</td>
<td>0.03</td>
<td>2.01</td>
</tr>
<tr>
<td>Grp Avg</td>
<td>0.07</td>
<td>0.12</td>
<td>0.62</td>
</tr>
<tr>
<td>Mean FU points</td>
<td>0.07</td>
<td>0.07</td>
<td>0.92</td>
</tr>
<tr>
<td>Other</td>
<td>0.05</td>
<td>0.09</td>
<td>0.55</td>
</tr>
<tr>
<td>Sample FU</td>
<td>-0.10</td>
<td>0.02</td>
<td>-4.40</td>
</tr>
<tr>
<td>Imputed</td>
<td>0.33</td>
<td>0.09</td>
<td>3.83</td>
</tr>
<tr>
<td>Unclear</td>
<td>0.02</td>
<td>0.02</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Note: generalized linear model with binary outcome.
Discussion

Across the 165 pharmacotherapy trials included in this analysis, less than half of the 74 studies reporting to have used an ITT strategy actually did so. This finding likely is due, at least in part, to a lack of a consensual definition of what constitutes an ITT analysis. In fact, the most common procedure for studies reporting, but not actually using an ITT, involved analyses on participants who completed a sufficient dose of treatment. That is, analyses were conducted on data for only those participants who completed a certain amount of treatment or who received a minimum intervention. This type of analysis is generally considered a "per protocol" approach, which contrasts to an ITT approach which includes outcome data for all participants, regardless of adherence to treatment. 2

Among the studies conducting a true ITT strategy, it was unclear what missing data strategy was used in nearly 25% of these studies. Lack of clarity in journal articles about how missing data were handled makes it difficult for readers to critically assess the study findings. A per protocol analysis answers questions of an explanatory nature, e.g., "how efficacious is this treatment for those adherent to the treatment?" In contrast, an ITT analysis provides more realistic estimates of the average treatment effects in the "real-world," as it accounts for both patient dropout and non-adherence to treatment. If findings from a per protocol analysis are incorrectly perceived as coming from an ITT analysis, treatment effects under more routine conditions of care will be overestimated. Journal editors and peer reviewers should be attentive to these issues and request that authors provide a clear description of the sample analyzed (i.e., ITT, modified ITT, per protocol) in their studies, along with details regarding how missing data were handled.
Because missing data strategies are becoming more sophisticated and are being facilitated by computer technology that is easily able to process data using complex algorithms, the diversity of missing data strategies that are employed is increasing in number. Indeed, our findings indicate that more complex imputation procedures are becoming more prevalent over time. One such imputation procedure is Multiple Imputation, which involves a Bayesian estimation procedure to average outcomes across multiple imputed datasets. Missing data are then replaced with a probable value based on other available variables in the data. Presumably, the results with this approach more closely approximate the results of an ITT analysis with 100% follow-up than any other method of handling missing data that is currently available.

Conclusion

Discrepancies in reporting versus actually conducting true ITT analyses were apparent in this body of alcohol pharmacotherapy trials. Lack of clarity regarding the missing data strategy used also was common. The degree to which these problems are present in reports of trials of pharmacotherapies and psychosocial interventions for other conditions remains to be determined. In addition, consensus on a standard definition of ITT is needed, as are clearer reporting standards for analyses and the handling of missing data in reports of clinical trials.
Acknowledgments

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Ethics

No ethics approval was required for completion of this study. It aggregated previously published journal articles.
ICMJE uniform disclosure

All authors have completed the ICMJE uniform disclosure form at

www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the

submitted work; no financial relationships with any organizations that might have an interest in

the submitted work in the previous three years; no other relationships or activities that could

appear to have influenced the submitted work.
Contributorship Information

A. C. Del Re was involved in the study's design, analysis and interpretation of data, drafting the article and revising it. Natalya C. Maisel was involved in the study's design and revising the article. Janet Blodgett was involved in the study's design. John W. Finney was involved in the study's conception and design, interpretation of data, and revising it critically for important intellectual content. All authors gave final approval of the version to be published.
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Article summary

Intention-to-Treat Analyses and Missing Data Approaches in Pharmacotherapy Trials for Alcohol Use Disorders

A. C. Del Re, Natalya C. Maisel, Janet Blodgett, John W. Finney

1) Article Focus

Using the reports of a large pool of randomized controlled trials, we examined:

- Linkage between analytic strategy (i.e., ITT or not)
- How missing data on outcomes were handled (if at all)
- Whether data analytic and missing data strategies have changed over time.

2) Key Messages

- Less than 40% of the studies actually conducted ITT
- The most common method utilized for studies reporting ITT, but not actually using one, involved analyses of data for participants who completed what was deemed a sufficient dose of treatment.
- Whereas no change in the use of ITT analyses over time was found, censored (last follow-up completed) and imputed missing data strategies have increased over time, while analyses of data only for the sample actually followed have decreased over time.

3) Strengths

- Examined a large body of RCT pharmacotherapy trials for alcohol misuse

Limitations

- Descriptive analyses could not determine whether there is any relationship between ITT and effect sizes
Intention-to-Treat Analyses and Missing Data Approaches in Pharmacotherapy Trials for Alcohol Use Disorders

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Primary Subject Heading: Research methods

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Keywords: STATISTICS & RESEARCH METHODS, CLINICAL PHARMACOLOGY, Substance misuse < PSYCHIATRY
Intention-to-Treat Analyses and Missing Data Approaches in Pharmacotherapy Trials for Alcohol Use Disorders

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Abstract

Objectives: Intention-to-treat (ITT) is an analytic strategy for reducing potential bias in treatment effects arising from missing data in randomized controlled trials (RCT). Currently, no universally accepted definition of ITT exists, although many researchers consider it to require either no attrition or some imputation procedure to account for missing outcome data in analyses.

Using the reports of a large pool of randomized controlled trials, we examined discrepancies between the types of analyses that alcohol pharmacotherapy researchers stated they used versus those they actually used. We also examined the linkage between analytic strategy (i.e., ITT or not) and how missing data on outcomes were handled (if at all), and whether data analytic and missing data strategies have changed over time.

Design: Descriptive statistics were generated for reported and actual data analytic strategy and for missing data strategy. In addition, generalized linear models determined changes over time in the use of ITT analyses and missing data strategies.

Setting: N/A

Participants: 165 RCTs of pharmacotherapy for alcohol use disorders.

Primary and secondary outcome measures: N/A

Results: Of the 165 studies, 74 reported using an ITT strategy. However, less than 40% of the studies actually conducted ITT according to the rigorous definition above. Whereas no change in the use of ITT analyses over time was found, censored (last follow-up completed) and imputed missing data strategies have increased over time, while analyses of data only for the sample actually followed have decreased.

Conclusions: Discrepancies in reporting versus actually conducting ITT analyses were found in this body of RCTs. Lack of clarity regarding the missing data strategy used was common. Consensus on a definition of ITT is important for adequate understanding of research findings.
Clearer reporting standards for analyses and the handling of missing data in pharmacotherapy trials and other intervention studies are needed.
In pharmacotherapy trials, participants typically are randomly assigned to a pharmacotherapy or a placebo (control) condition. With a sufficient sample size, randomization usually produces separate groups without systematic differences by equalizing factors within groups that may be associated with outcome (e.g., motivation, age, gender). Under ideal circumstances, the randomization process allows valid causal inferences to be made about the impact of the pharmacotherapy compared to the control condition. That is, one can be highly confident that any post-treatment differences in outcome are attributable to the impact of the medication itself and not to pre-existing differences in the characteristics of the pharmacotherapy and placebo samples. However, when the randomization process is disrupted, either through treatment dropout and/or missing data on outcomes, or when the original sample as randomized is not the same sample analyzed (analyzed N < randomized N), bias may be introduced that compromises the internal validity of results. [1–4]

The intention-to-treat (ITT) analytic strategy is one solution for eliminating or reducing bias in treatment effects arising from missing outcome data in randomized controlled trials (RCTs). [1,2] Although no universally accepted definition of ITT currently exists, the procedure nevertheless is endorsed in the Consolidated Standards for Reporting Trials (CONSORT). [5–7] One particularly succinct definition of a "true ITT" [8] analysis is "once randomized, always analyzed." [9] Under this definition, ITT involves analysis of all trial participants who were randomized, regardless of adherence to treatment protocol (e.g., dropout/withdrawal or protocol deviations). In other words, defined this way, ITT requires either no attrition or some imputation procedure to account for any missing data.

ITT has several strengths, including (1) helping to preserve the integrity of the randomization process (i.e., groups are expected to be similar except for random variation and
receipt of treatment/control condition) and (2) providing a more realistic estimate of average treatment effects in the "real-world" as it is the norm for some patients to dropout or not adhere to treatment. [1] Both points above address the issue of patient dropout, as analyses on only adherent patients likely would lead to inflated estimates of treatment effects. Research has shown that adherent patients generally do better than non-adherent patients, regardless of treatment. [10,11] The more realistic estimates of treatment effects under conditions of routine care that are derived from ITT analyses have particular relevance for policy makers and those interested in hypotheses of pragmatic ("real world") importance.

A variant of the ITT approach, what Polit and Gillespie (2010) term a “modified ITT” analysis, maintains the conditions to which people were randomly assigned and attempts to follow-up all participants, regardless of their participation in the intervention. However, only those successfully followed are included in the analyses. With this modified approach, however, the balance in pre-existing characteristics across conditions sought through random assignment is less likely to hold.

An alternative to ITT analysis, the per protocol analytic procedure (i.e., analyses based on only “adherent” participants in randomized samples), has strengths as well and is of particular importance for hypotheses of an explanatory nature.[12] The per protocol approach can range from analyses in which only those research participants who began treatment are included, to those in which only participants who received what was deemed a “sufficient dose” of treatment are used, to those in which only participants who fully completed treatment are included also referred to as a ‘complete cases’ approach[also referred to as a ‘complete cases’ approach; 2]. Advocates of per protocol approach assert that the analysis tests the true efficacy of the
intervention when used as directed (i.e., efficacy among those who are adherent and able to
tolerate the treatment).

Because both ITT and per protocol approaches to RCT analyses have their strengths, a
possible strategy is to conduct an ITT analysis, with a per protocol sensitivity analysis to
“bracket” likely effects under different conditions. Nevertheless, ITT analyses are considered
the "gold standard" and researchers frequently report the use of this procedure in published
literature, even in the absence of a consensual definition. Discrepancies can arise, however,
between the type of analyses researchers state in research reports that they conducted and what
they actually did with respect to use of a “true” ITT analysis or some other procedure based on
less than the full randomized sample. For example, in clinical trials in the nursing field, Polit
and Gillespie (2009) found that for 10.5% of studies, researchers who stated they had used an
ITT approach had actually conducted per protocol analyses.

It is unknown to what degree ITT strategies are being employed in pharmacotherapy for
alcohol use disorders. One aim of this review was to determine if there are discrepancies between
the types of analyses that researchers stated they used and those they actually used, based on
information in reports of a large pool of randomized controlled trials of pharmacotherapy for
alcohol use disorders published between 1970 to 2009. A second aim was to describe the use of
different missing data strategies in studies in which true and modified ITT analyses were and
were not conducted. The final aim was to determine whether the use of different data analytic
approaches and certain types of missing data approaches (e.g., multiple imputation) has
increased over time while the use of others has decreased.

**Methods**

**Literature Search**
As part of a larger project examining the efficacy of pharmacotherapies for alcohol use disorders and alcohol misuse, [i.e., 13] we identified relevant randomized controlled trials via several searches of PubMed and PsycINFO conducted at different points over the past decade. Study inclusion criteria were (a) a focus on treating alcohol misuse or an alcohol use disorder; (b) participants 18 years of age or older; (c) publication between 1970 and 2009; (d) a report in the English language; and (e) random assignment of at least five participants each to medication and placebo groups. The details of inclusion/exclusion criteria can be found in Maisel et al.[12]

Searches were intermittent due to sporadic availability of funds and resources. For example, in one search we used search terms for various medications (e.g., “naltrexone”), terms for alcohol problems and use disorders and alcohol misuse (e.g., “alcohol*,” “problem drinking”) and terms for randomized controlled trials (e.g., “randomized controlled,” “clinical trial”). This search yielded 1,602 potential research reports. Based on examination of abstracts and, in some cases, full text versions of these reports, 1,184 were identified as not relevant (e.g., qualitative studies, reviews). Of the remaining articles, 215 were rejected based on not meeting our eligibility criteria (e.g., open-label trial), 138 articles met the inclusion criteria, but 65 were additional publications for studies already in the dataset (e.g., reporting secondary analyses). In addition to the database searches, we pursued the reference sections from the reports of the included studies and from previously published reviews of this literature. For the present analysis, a total of 165 studies met our inclusion criteria

Variables

Descriptive and inferential statistics were generated for two categorical variables: (1) sample analyzed and (2) missing data strategy. The categories of the “sample analyzed” variable were:
(1) Full random sample - analyses involved the total randomized N’s (with or without imputation of missing data)

(2) Full random sample (likely) - analyses appeared to use the full randomized sample, but N’s were not reported

(3) Random sample followed-up - attempted to follow-up all randomized participants regardless of amount of medication/treatment completed and conducted analyses on this sample

(4) Sufficient dose - analyses were conducted for only those participants who completed a specified amount of treatment or who received at least a minimum dose of treatment

(5) Completer sample - analyses conducted for only those patients who completed the medication/treatment phase

(6) False inclusion - after randomization, participants were found to not meet inclusion criteria and were subsequently removed from the analyses

(7) Other - reported N’s or degrees of freedom that were less than what would be expected for the randomized N, but no explanation of the participants included or excluded from the analysis was provided

(8) Unclear – insufficient information was provided to determine the sample analyzed.

Only analyses conducted on the Full Random Sample or Full Random Sample (likely) categories were deemed to be “true” ITT analyses, whereas the others were considered something other than ITT analyses.

The categories for the “missing data strategy” variable were as follows:

(1) No dropout – no dropout from treatment and 100% reassessed

The categories for the “missing data strategy” variable were as follows:
(2) All followed - there were drop-outs from treatment, but all participants, including treatment dropouts, were reassessed

(3) Statistical imputation or interpolation - used a statistical analysis that imputed or interpolated missing data, e.g., mixed-model interpolation

(4) Failure assumed for missing data (missing = failure) - assumed that missing data reflected poor outcome, e.g., relapse

(5) Baseline assigned - a participant’s baseline score was assigned if outcome data were missing

(6) LOCF - used the imputation strategy of Last Observation Carried Forward

(7) Censored – last assessment point was used in survival analyses

(8) Mean - used the mean of the sample followed for missing data

(9) Other – used some other imputation of missing data strategy

(10) Sample followed - conducted analyses with data for the sample of participants that the researchers were able to follow/reassess

(11) Unclear - no or unclear information provided.

Statistical Analyses

Descriptive statistics were generated for data analytic strategies and missing data strategies used in the 165 RCTs of pharmacotherapies for AUD and alcohol misuse. Generalized linear model analyses were conducted to determine changes in both data analytic and missing data strategy over time. In those analyses, the response variables, data analytic strategy and missing data strategy, were coded as binary (0='No', 1='Yes'), with year of publication as predictor of a 'Yes' response.

Results
As noted in Table 1, a substantial discrepancy was evident between reporting an ITT strategy versus actually conducting a “true” ITT analysis (i.e., reporting an ITT strategy when something other than ITT was conducted). Of the 165 studies included in this review, 74 reported using an ITT strategy. However, less than half of those studies conducted a true ITT analysis ($K=29; 39\%$) according to information in study reports. Interestingly, 35% ($K=32$) of the 91 studies whose reports made no claim of using an ITT strategy, in fact, did perform true ITT analyses.
Table 1.

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<td>Full Random Sample</td>
<td>Full Random Sample (likely)</td>
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<td>No ((K=91))</td>
<td>32 (35%)</td>
<td>28 (25%)</td>
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<td>Yes ((K=74))</td>
<td>29 (39%)</td>
<td>21 (28%)</td>
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<tr>
<td>Total ((K=165))</td>
<td>61 (37%)</td>
<td>49 (29%)</td>
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Note: \(a\)ITT=Full Random Sample or Full Random Sample (likely) categories; \(K=\)study, column description: (1) Full random sample (analyses involved the total randomized N’s), (2) Full random sample (likely) (appears to be using the full randomized sample, but N’s are not reported with analyses), (3) Random sample followed-up (attempted to follow-up all randomized participants regardless of amount of medication/treatment completed, and conducted analyses on this sample), (4) Sufficient dose (analyses conducted on only those participants who received a minimum amount of medication/treatment), (5) Completer sample (analyses conducted on only those patients who completed the medication/treatment phase), (6) False inclusion (after randomization, participant is found to not meet inclusion criteria and is subsequently removed from the analyses), (7) Other (analyses report N’s or degrees of freedom that are less than what would be expected for the randomized N, but no explanation on the participants included or excluded from the analysis is provided), and (8) Unclear (insufficient information to determine the sample analyzed). Only categories (1) Full random sample and (2) Full random sample (likely) are considered a “true” ITT strategy, whereas the others are considered something other than ITT.
Regarding the specific data analytic strategy used, the values in each row of Table 1 do not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming failure for dichotomous outcomes AND also used a complete cases approach for continuous outcomes). In such instances, we coded "Reported Using ITT" as "Yes" if the study mentioned using an ITT strategy and coded it as "No" otherwise (i.e., no mention of using an ITT strategy).

The most common approach utilized in studies reporting the use of an ITT strategy, other than use of a true ITT ($K=29; 39\%$), involved analyses of data for participants who completed a “sufficient dose” of the medication/treatment ($K=40; 39\%$). All other strategies were utilized <10\% of the time. The most common analytic method used in studies not mentioning an ITT strategy was actually a true ITT analysis ($K=32; 29\%$), followed by analyses of data from completer samples ($K=31; 28\%$), analyses for participants who completed a “sufficient dose” of medication/treatment ($K=19; 17\%$), and indeterminable strategies (i.e., Unclear; $K=16; 14\%$).

Table 2 reports the descriptive information on the missing data strategies employed in the studies using and not using a true ITT approach. Similar to Table 1, the values in each row of Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due to 42 studies utilizing multiple missing data strategies. The most common missing data strategy utilized in studies employing an ITT approach was either unclear ($K=24; 23\%$) or involved censoring data at the end of FU procedure in survival analyses ($K=23; 22\%$). A study could be categorized as employing an ITT strategy, but having an unclear missing data strategy if, for example, the study reported the full randomized $N$s from analyses, but it was unclear what particular missing data strategy was utilized. The next most frequently used strategies were
assuming missing equals relapse or some other poor outcome ("Failure"; \( K = 14 \); 13%) and using a statistical imputation or interpolation strategy (\( K = 14 \); 13%), such as a mixed effects model. All other missing data strategies were utilized \( \leq 10\% \) of the time, except the last observation carried forward (LOCF) procedure that was used in \( K = 12 \) 11% of the studies.
Table 2.

<table>
<thead>
<tr>
<th>Conducted True ITT</th>
<th>Missing Data Strategy</th>
<th>No Tx or FU Dropout</th>
<th>All FU (some tx dropout)</th>
<th>Imputation or Interpolation</th>
<th>Missing = Failure</th>
<th>Baseline Assigned</th>
<th>LOCF</th>
<th>Censored (end of FU) Survival Analysis</th>
<th>Mean Substituted</th>
<th>Other</th>
<th>Sample FU</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (K=104)</td>
<td></td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>23</td>
<td>1</td>
<td>22</td>
<td>25</td>
<td>3</td>
<td>2</td>
<td>38</td>
<td>17</td>
</tr>
<tr>
<td>Yes (K=61)</td>
<td></td>
<td>1</td>
<td>2</td>
<td>14</td>
<td>14</td>
<td>1</td>
<td>12</td>
<td>23</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>Total (K=165)</td>
<td></td>
<td>1 (&gt;1%)</td>
<td>2 (&gt;1%)</td>
<td>20</td>
<td>37</td>
<td>2</td>
<td>34</td>
<td>48</td>
<td>5</td>
<td>3</td>
<td>49</td>
<td>41</td>
</tr>
</tbody>
</table>

Note. Column description: (1) No dropout, (2) Followed-up (some dropout) (there were drop-outs from treatment, but all participants, including dropouts were followed-up), (3) Interpolated (used a statistical analysis that interpolated missing data, e.g., mixed-model interpolation), (4) Failure (assumed that missing data = failure, e.g., relapse), (5) Baseline assigned (assigned a person’s baseline score if the outcome score was missing), (6) LOCF (used an imputation strategy of Last Observation Carried Forward), (7) Censored (end of FU) (data presented in a survival analysis), (8) Mean (used the mean for each person across available assessments/timepoints), (9) Other (other imputation strategy), (10) Sample FU (conducted analyses on the sample of participants that the researchers was able to follow-up), (11) Unclear (no information provided/unclear).
The most common missing data method utilized in studies not conducting a true ITT analysis was analyzing the sample followed-up ($K=38; 27\%$), followed by censoring at the end of FU procedure ($K=25; 18\%$), assuming failure (“Failure”; $K=23; 17\%$), last observation carried forward ($K=23; 16\%$) and an unclear strategy ($K=17; 12\%$). All other missing data strategies were used $\leq 10\%$ of the time. A study could be categorized as not employing an ITT strategy, but still using a missing data strategy of assuming failure or last observation carried forward if, for example, the study assumed failure for missing participants, but something less than the full randomized $N$s were reported for analyses. Tables 3 and 4 display changes in ITT analyses and missing data strategies over time. No statistically significant change (although marginally significant trend) was found in use of true ITT analyses over time (Table 3). This relationship is depicted graphically with time on the $x$-axis, probability (of being an ITT) from generalized linear model results on the $y$-axis, and raw study values ($0=$ not ITT, $1=$ITT) displayed as points. The 95% confidence intervals are displayed as a grey line around the probability slope.

Several statistically significant relationships between missing data strategy and time emerged, as displayed in Table 4. Specifically, censored at end of FU (for survival analyses), last observation carried forward (LOCF), and using a statistical analysis to impute/interpolate missing data (Imputed/Interpolated, e.g., mixed-model interpolation) have become more common over time, whereas analyses conducted on only the samples of participants that the researchers were able to follow-up (Sample FU) has become less common. To explore whether increasing use of certain missing data strategies over time was confounded with longitudinal methods being increasingly employed, a proxy dummy control variable ($0=$only end-of treatment
assessment, 1= posttreatment and follow-up assessment(s)) was added to the analyses; the results were virtually unchanged.
**Table 3. Change in true ITT analyses over time**

<table>
<thead>
<tr>
<th>Estimate</th>
<th>SE</th>
<th>t-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-1.52</td>
<td>0.64</td>
<td>-2.39</td>
</tr>
<tr>
<td>Year</td>
<td>0.04</td>
<td>0.02</td>
<td>1.85</td>
</tr>
</tbody>
</table>

Note: generalized linear model with binary outcome (ITT analyses conducted=1 or not=0). *=p-value <.05

k=165

**Table 4. Change in missing data strategy over time**

<table>
<thead>
<tr>
<th>Estimate</th>
<th>SE</th>
<th>z-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fail</td>
<td>0.03</td>
<td>0.02</td>
<td>1.38</td>
</tr>
<tr>
<td>All FU</td>
<td>-0.10</td>
<td>0.09</td>
<td>-1.18</td>
</tr>
<tr>
<td>All FU (some dropout)</td>
<td>-0.09</td>
<td>0.06</td>
<td>-1.43</td>
</tr>
<tr>
<td>Baseline Assigned</td>
<td>0.47</td>
<td>0.36</td>
<td>1.31</td>
</tr>
<tr>
<td>Censored (end of FU)</td>
<td>0.09</td>
<td>0.03</td>
<td>3.19</td>
</tr>
<tr>
<td>LOCF</td>
<td>0.06</td>
<td>0.03</td>
<td>2.01</td>
</tr>
<tr>
<td>Grp Avg</td>
<td>0.07</td>
<td>0.12</td>
<td>0.62</td>
</tr>
<tr>
<td>Mean FU points</td>
<td>0.07</td>
<td>0.07</td>
<td>0.92</td>
</tr>
<tr>
<td>Other</td>
<td>0.05</td>
<td>0.09</td>
<td>0.55</td>
</tr>
<tr>
<td>Sample FU</td>
<td>-0.10</td>
<td>0.02</td>
<td>-4.40</td>
</tr>
<tr>
<td>Interpolation</td>
<td>0.33</td>
<td>0.09</td>
<td>3.83</td>
</tr>
<tr>
<td>Unclear</td>
<td>0.02</td>
<td>0.02</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Note: generalized linear model with binary outcome.

*=p-value <.05
Discussion

Across the 165 pharmacotherapy trials included in this analysis, less than half of the 74 studies reporting to have used an ITT strategy actually did so. This finding likely is due, at least in part, to a lack of a consensual definition of what constitutes an ITT analysis. In fact, the most common procedure for studies reporting, but not actually using an ITT, involved analyses on participants who completed a sufficient dose of treatment. That is, analyses were conducted on data for only those participants who completed a certain amount of treatment or who received a minimum intervention. This type of analysis is generally considered a "per protocol" approach, which contrasts to an ITT approach which includes outcome data for all participants, regardless of adherence to treatment [2].

Among the studies conducting a true ITT strategy, it was unclear what missing data strategy was used in nearly 25% of these studies. Lack of clarity in journal articles about how missing data were handled makes it difficult for readers to critically assess the study findings. A per protocol analysis answers questions of an explanatory nature, e.g., "how efficacious is this treatment for those adherent to the treatment?" In contrast, an ITT analysis provides more realistic (and usually less biased) estimates of the average treatment effects in the "real-world," as it accounts for both patient dropout and non-adherence to treatment. If findings from a per protocol analysis are incorrectly perceived as coming from an ITT analysis, treatment effects under more routine conditions of care will be overestimated. Journal editors and peer reviewers should be attentive to these issues and request that authors provide a clear description of the sample analyzed (i.e., ITT, modified ITT, per protocol) in their studies, along with details regarding how missing data were handled.
Because missing data strategies are becoming more sophisticated and are being facilitated by computer technology that is easily able to process data using complex algorithms, the diversity of missing data strategies that are employed is increasing. Indeed, our findings indicate that more complex imputation procedures are becoming more prevalent over time. One such imputation procedure is Multiple Imputation, [3] which involves a Bayesian estimation procedure to average outcomes across multiple imputed datasets. Missing data are then replaced with a probable value based on other available variables in the data. Presumably, the results with this approach more closely approximate the results of an ITT analysis with 100% follow-up than any other method of handling missing data that is currently available.

Conclusion

Discrepancies in reporting versus actually conducting true ITT analyses were apparent in this body of alcohol pharmacotherapy trials. Lack of clarity regarding the missing data strategy used also was common. The degree to which these problems are present in reports of trials of pharmacotherapies and psychosocial interventions for other conditions remains to be determined. In addition, consensus on a standard definition of ITT is needed, as are clearer reporting standards for analyses and the handling of missing data in reports of clinical trials.
Acknowledgments

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Ethics

No ethics approval was required for completion of this study. It aggregated previously published journal articles.
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Contributorship Information

A. C. Del Re was involved in the study's design, analysis and interpretation of data, drafting the article and revising it. Natalya C. Maisel was involved in the study's design and revising the article. Janet Blodgett was involved in the study's design. John W. Finney was involved in the study's conception and design, interpretation of data, and revising it critically for important intellectual content. All authors gave final approval of the version to be published.
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Article summary

Intention-to-Treat Analyses and Missing Data Approaches in Pharmacotherapy Trials for Alcohol Use Disorders

A. C. Del Re, Natalya C. Maisel, Janet Blodgett, John W. Finney

1) Article Focus

Using the reports of a large pool of randomized controlled trials, we examined:

- Linkage between analytic strategy (i.e., ITT or not)
- How missing data on outcomes were handled (if at all)
- Whether data analytic and missing data strategies have changed over time.

2) Key Messages

- Less than 40% of the studies actually conducted ITT
- The most common method utilized for studies reporting ITT, but not actually using one, involved analyses of data for participants who completed what was deemed a sufficient dose of treatment.
- Whereas no change in the use of ITT analyses over time was found, censored (last follow-up completed) and imputed missing data strategies have increased over time, while analyses of data only for the sample actually followed have decreased over time.

3) Strengths

- Examined a large body of RCT pharmacotherapy trials for alcohol misuse

Limitations

- Descriptive analyses could not determine whether there is any relationship between ITT and effect sizes
Intention-to-Treat Analyses and Missing Data Approaches in Pharmacotherapy Trials for Alcohol Use Disorders

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Abstract

Objectives: Intention-to-treat (ITT) is an analytic strategy for reducing potential bias in treatment effects arising from missing data in randomized controlled trials (RCT). Currently, no universally accepted definition of ITT exists, although many researchers consider it to require either no attrition or some imputation procedure to account for missing outcome data in analyses.

Using the reports of a large pool of randomized controlled trials, we examined discrepancies between the types of analyses that alcohol pharmacotherapy researchers stated they used versus those they actually used. We also examined the linkage between analytic strategy (i.e., ITT or not) and how missing data on outcomes were handled (if at all), and whether data analytic and missing data strategies have changed over time.

Design: Descriptive statistics were generated for reported and actual data analytic strategy and for missing data strategy for 165 RCTs of pharmacotherapy for alcohol use disorders (AUDs). In addition, generalized linear models determined changes over time in the use of ITT analyses and missing data strategies.

Setting: N/A

Participants: 165 RCTs of pharmacotherapy for alcohol use disorders.

Primary and secondary outcome measures: N/A

Results: Of the 165 studies, 74 reported using an ITT strategy. However, based on their reports, less than 40% of the studies actually conducted ITT according to the rigorous definition above.

The most common method utilized for studies reporting ITT, but not actually using one, involved analyses of data for participants who completed what was deemed a sufficient dose of treatment.

Whereas no change in the use of ITT analyses over time was found, censored (last follow-up completed) and imputed missing data strategies have increased over time, while analyses of data only for the sample actually followed have decreased over time.
Conclusions: Discrepancies in reporting versus actually conducting ITT analyses were found in this body of RCTs. Lack of clarity regarding the missing data strategy used was common. Consensus on a definition of ITT is important for adequate understanding of research findings. Clearer reporting standards for analyses and the handling of missing data in pharmacotherapy trials and other intervention studies are needed.
In pharmacotherapy trials, participants typically are randomly assigned to a pharmacotherapy or a placebo (control) condition. With a sufficient sample size, randomization usually produces separate groups without systematic differences by equalizing factors within groups that may be associated with outcome (e.g., motivation, age, gender). Under ideal circumstances, the randomization process allows valid causal inferences to be made about the impact of the pharmacotherapy compared to the control condition. That is, one can be highly confident that any post-treatment differences in outcome are attributable to the impact of the medication itself and not to pre-existing differences in the characteristics of the pharmacotherapy and placebo samples. However, when the randomization process is disrupted, either through treatment dropout and/or missing data on outcomes, or when the original sample as randomized is not the same sample analyzed (analyzed N < randomized N), bias may be introduced that compromises the internal validity of results. [1–4]

The intention-to-treat (ITT) analytic strategy is one solution for eliminating or reducing bias in treatment effects arising from missing outcome data in randomized controlled trials (RCTs). [1,2] Although no universally accepted definition of ITT currently exists, the procedure nevertheless is endorsed in the Consolidated Standards for Reporting Trials (CONSORT). [5–7]

One particularly succinct definition of a “true ITT” [8] analysis is “once randomized, always analyzed.” (Schulz and Grimes, 2002, p. 781). Under this definition, ITT involves analysis of all trial participants who were randomized, regardless of adherence to treatment protocol (e.g., dropout/withdrawal or protocol deviations). In other words, defined this way, ITT requires either no attrition or some imputation procedure to account for any missing data.

ITT has several strengths, including (1) helping to preserve the integrity of the randomization process (i.e., groups are expected to be similar except for random variation and
receipt of treatment/control condition) and (2) providing a more realistic estimate of average
treatment effects in the "real-world" as it is the norm for some patients to dropout or not adhere
to treatment. [1] Both points above address the issue of patient dropout, as analyses on only
adherent patients likely would lead to inflated estimates of treatment effects. Research has shown
that adherent patients generally do better than non-adherent patients, regardless of treatment.
[10,11] (Avins et al., 2010; Granger et al., 2006). The more realistic estimates of treatment effects
under conditions of routine care that are derived from ITT analyses have particular relevance for
policy makers and those interested in hypotheses of pragmatic ("real world") importance.

A variant of the ITT approach, what Polit and Gillespie (2010) term a “modified ITT”
analysis, maintains the conditions to which people were randomly assigned and attempts to
follow-up all participants, regardless of their participation in the intervention. However, only
those successfully followed are included in the analyses. With this modified approach, however,
the balance in pre-existing characteristics across conditions sought through random assignment is
less likely to hold.

An alternative to ITT analysis, the per protocol analytic procedure (i.e., analyses based
on only “adherent” participants in randomized samples), has strengths as well and is of particular
importance for hypotheses of an explanatory nature [12] (Schwartz and Lellouch, 1967). The per
protocol approach can range from analyses in which only those research participants who began
treatment are included, to those in which only participants who received what was deemed a
“sufficient dose” of treatment are used, to those in which only participants who fully completed
treatment are included also referred to as a ‘complete cases’ approach [also referred to as a
‘complete cases’ approach; 2]. Advocates of per protocol approach assert that the analysis tests
the true efficacy of the intervention when used as directed (i.e., efficacy among those who are adherent and able to tolerate the treatment).

Because both ITT and per protocol approaches to RCT analyses have their strengths, a possible strategy is to conduct an ITT analysis, with a per protocol sensitivity analysis to “bracket” likely effects under different conditions. Nevertheless, ITT analyses are considered the "gold standard" and researchers frequently report the use of this procedure in published literature, even in the absence of a consensual definition. Discrepancies can arise, however, between the type of analyses researchers state in research reports that they conducted and what they actually did with respect to use of a “true” ITT analysis or some other procedure based on less than the full randomized sample. For example, in clinical trials in the nursing field, Polit and Gillespie (2009) found that for 10.5% of studies, researchers who stated they had used an ITT approach had actually conducted per protocol analyses.

It is unknown to what degree ITT strategies are being employed in pharmacotherapy for alcohol use disorders. One aim of this review was to determine if there are in this review, we examined discrepancies between the types of analyses that researchers stated they used and those they actually used, based on information in reports of a large pool of randomized controlled trials of pharmacotherapy for alcohol use disorders published between 1970 to 2009. A second aim was to describe. We also examined the use of different missing data strategies in studies in which true and modified ITT analyses were and were not conducted. The final aim was to determine Finally, we examined whether the use of different data analytic approaches and certain types of missing data approaches (e.g., multiple imputation) has increased over time while the use of others has decreased.

Methods

Literature Search
As part of a larger project examining the efficacy of pharmacotherapies for alcohol use disorders and alcohol misuse, we identified relevant randomized controlled trials via several searches of PubMed and PsycINFO conducted at different points over the past decade. Study inclusion criteria were (a) a focus on treating alcohol misuse or an alcohol use disorder; (b) participants 18 years of age or older; (c) publication between 1970 and 2009; (d) a report in the English language; and (e) random assignment of at least five participants each to medication and placebo groups. The details of inclusion/exclusion criteria can be found in Maisel et al.[12]

Searches were intermittent due to sporadic availability of funds and resources. For example, in one search we used search terms for various medications (e.g., “naltrexone”), terms for alcohol problems and use disorders and alcohol misuse (e.g., “alcohol*,” “problem drinking”) and terms for randomized controlled trials (e.g., “randomized controlled,” “clinical trial”). This search yielded 1,602 potential research reports. Based on examination of abstracts and, in some cases, full text versions of these reports, 1,184 were identified as not relevant (e.g., qualitative studies, reviews). Of the remaining articles, 215 were rejected based on not meeting our eligibility criteria (e.g., open-label trial), 138 articles met the inclusion criteria, but 65 were additional publications for studies already in the dataset (e.g., reporting secondary analyses). In addition to the database searches, we pursued the reference sections from the reports of the included studies and from previously published reviews of this literature. For the present analysis, a total of 165 studies met our inclusion criteria

Variables

Descriptive and inferential statistics were generated for two categorical variables: (1) sample analyzed and (2) missing data strategy. The categories of the “sample analyzed” variable were:
(1) Full random sample - analyses involved the total randomized N’s (with or without imputation of missing data)

(2) Full random sample (likely) - analyses appeared to use the full randomized sample, but N’s were not reported

(3) Random sample followed-up - attempted to follow-up all randomized participants regardless of amount of medication/treatment completed and conducted analyses on this sample

(4) Sufficient dose - analyses were conducted for only those participants who completed a specified amount of treatment or who received at least a minimum dose of treatment

(5) Completer sample - analyses conducted for only those patients who completed the medication/treatment phase

(6) False inclusion - after randomization, participants were found to not meet inclusion criteria and were subsequently removed from the analyses

(7) Other - reported N’s or degrees of freedom that were less than what would be expected for the randomized N, but no explanation of the participants included or excluded from the analysis was provided

(8) Unclear – insufficient information was provided to determine the sample analyzed.

Only analyses conducted on the Full Random Sample or Full Random Sample (likely) categories were deemed to be “true” ITT analyses, whereas the others were considered something other than ITT analyses.

The for those studies in which ITT analyses were actually conducted (i.e., “true” ITT with no missing outcome data due to 100% reassessment rate or imputing missing data), the categories for the “missing data strategy” variable were as follows:
(1) No dropout – no dropout from treatment and 100% reassessed

(2) All followed - there were drop-outs from treatment, but all participants, including treatment dropouts, were reassessed

(3) Statistical imputation or interpolation - used a statistical analysis that imputed or interpolated missing data, e.g., mixed-model interpolation imputation

(4) Failure assumed for missing data (missing = failure) - assumed that missing data reflected poor outcome, e.g., relapse

(5) Baseline assigned - a participant’s baseline score was assigned if outcome data were missing

(6) LOCF - used the imputation strategy of Last Observation Carried Forward

(7) Censored – last assessment point was used in survival analyses

(8) Mean - used the mean of the sample followed for missing data

(9) Other – used some other imputation of missing data strategy

(10) Sample followed - conducted analyses with data for the sample of participants that the researchers were able to follow/reassess

(11) Unclear - no or unclear information provided.

**Statistical Analyses**

Descriptive statistics were generated for data analytic strategies and missing data strategies used in the 165 RCTs of pharmacotherapies for AUD and alcohol misuse. Generalized linear model analyses were conducted to determine changes in both data analytic and missing data strategy over time. In those analyses, the response variables, data analytic strategy and missing data strategy, were coded as binary (0='No', 1='Yes'), with year of publication as predictor of a 'Yes' response.
Results

As noted in Table 1, a substantial discrepancy was evident between reporting an ITT strategy versus actually conducting a “true” ITT analysis (i.e., reporting an ITT strategy when something other than ITT was conducted). Of the 165 studies included in this review, 74 reported using an ITT strategy. However, less than half of those studies conducted a true ITT analysis ($K=29; 39\%$) according to information in study reports. Interestingly, 35% ($K=32$) of the 91 studies whose reports made no claim of using an ITT strategy, in fact, did perform true ITT analyses.
Table 1.

<table>
<thead>
<tr>
<th>Reported Using ITT</th>
<th>Conducted True ITT*</th>
<th>Sample Analyzed</th>
<th>Total Number of IIT and/or Non-ITT Approaches Used</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Full Random Sample</td>
<td>Full Random Sample (likely)</td>
</tr>
<tr>
<td>No (K=91)</td>
<td></td>
<td>32 (35%)</td>
<td>28 (25%)</td>
</tr>
<tr>
<td>Yes (K=74)</td>
<td></td>
<td>29 (39%)</td>
<td>21 (21%)</td>
</tr>
<tr>
<td>Total (K=165)</td>
<td></td>
<td>61 (37%)</td>
<td>49 (23%)</td>
</tr>
</tbody>
</table>

Note: *ITT=Full Random Sample or Full Random Sample (likely) categories; K=study, column description: (1) Full random sample (analyzes involved the total randomized N’s), (2) Full random sample (likely) (appears to be using the full randomized sample, but N’s are not reported with analyses), (3) Random sample followed-up (attempted to follow-up all randomized participants regardless of amount of medication/treatment completed, and conducted analyses on this sample), (4) Sufficient dose (analyzes conducted on only those participants who received a minimum amount of medication/treatment), (5) Completer sample (analyzes conducted on only those patients who completed the medication/treatment phase), (6) False inclusion (after randomization, participant is found to not meet inclusion criteria and is subsequently removed from the analyses), (7) Other (analyzes report N’s or degrees of freedom that are less than what would be expected for the randomized N, but no explanation on the participants included or excluded from the analysis is provided), and (8) Unclear (insufficient information to determine the sample analyzed). Only categories (1) Full random sample and (2) Full random sample (likely) are considered a “true” ITT strategy, whereas the others are considered something other than ITT.
Regarding the specific data analytic strategy used, the values in each row of Table 1 do not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming failure for dichotomous outcomes AND also used a complete cases approach for continuous outcomes). In such instances, we coded "Reported Using ITT" as "Yes" if the study mentioned using an ITT strategy and coded it as "No" otherwise (i.e., no mention of using an ITT strategy).

The most common approach utilized in studies reporting the use of an ITT strategy, other than use of a true ITT (K=29; 39%), involved analyses of data for participants who completed a “sufficient dose” of the medication/treatment (K=40; 39%). All other strategies were utilized <10% of the time. The most common analytic method used in studies not mentioning an ITT strategy was actually a true ITT analysis (K=32; 29%), followed by analyses of data from completer samples (K=31; 28%), analyses for participants who completed a “sufficient dose” of medication/treatment (K=19; 17%), and indeterminable strategies (i.e., Unclear; K=16; 14%).

Table 2 reports the descriptive information on the missing data strategies employed in the studies using and not using a true ITT approach. Similar to Table 1, the values in each row of Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due to 42 studies utilizing multiple missing data strategies. The most common missing data strategy utilized in studies employing an ITT approach was either unclear (K=24; 23%) or involved censoring data at the end of FU procedure in survival analyses (K=23; 22%). A study could be categorized as employing an ITT strategy, but having an unclear missing data strategy if, for example, the study reported the full randomized Ns from analyses, but it was unclear what particular missing data strategy was utilized. The next most frequently used strategies were
assuming missing equals relapse or some other poor outcome (“Failure”; K=14; 13%) and using a statistical imputation or interpolation strategy (K=14; 13%), such as a mixed effects model. All other missing data strategies were utilized ≤10% of the time, except the last observation carried forward (LOCF) procedure that was used in (K=12) 11% of the studies.
### Table 2.
Conducted True ITT

<table>
<thead>
<tr>
<th>Missing Data Strategy</th>
<th>No Tx or FU (some tx dropout)</th>
<th>All FU (some tx dropout)</th>
<th>Imputation</th>
<th>Interpolation</th>
<th>Baseline Assigned</th>
<th>LOCF</th>
<th>Censored (end of FU)</th>
<th>Survival Analysis</th>
<th>Mean Substituted</th>
<th>Other</th>
<th>Sample FU</th>
<th>Unclear</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No</strong> (K=104)</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>23</td>
<td>1</td>
<td>22</td>
<td>25</td>
<td>3</td>
<td>2</td>
<td>38</td>
<td>17</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(4%)</td>
<td></td>
<td>(17%)</td>
<td>(1%)</td>
<td>(16%)</td>
<td>(18%)</td>
<td>(1%)</td>
<td>(2%)</td>
<td>(1%)</td>
<td>(27%)</td>
<td>(12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Yes</strong> (K=61)</td>
<td>1</td>
<td>2</td>
<td>14</td>
<td>14</td>
<td>1</td>
<td>12</td>
<td>23</td>
<td>2</td>
<td>1</td>
<td>11</td>
<td>24</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1%)</td>
<td>(2%)</td>
<td>(13%)</td>
<td>(13%)</td>
<td>(1%)</td>
<td>(11%)</td>
<td>(22%)</td>
<td>(2%)</td>
<td>(1%)</td>
<td>(10%)</td>
<td>(23%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong> (K=165)</td>
<td>1</td>
<td>2</td>
<td>20</td>
<td>37</td>
<td>2</td>
<td>34</td>
<td>48</td>
<td>5</td>
<td>3</td>
<td>49</td>
<td>41</td>
<td>259a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(&gt;1%)</td>
<td>(&gt;1%)</td>
<td>(07%)</td>
<td>(16%)</td>
<td>(&gt;1%)</td>
<td>(13%)</td>
<td>(19%)</td>
<td>(2%)</td>
<td>(1%)</td>
<td>(19%)</td>
<td>(16%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Column description: (1) No dropout, (2) Followed-up (some dropout) (there were drop-outs from treatment, but all participants, including dropouts were followed-up), (3) Interpolated/Imputed (used a statistical analysis that interpolated/imputed missing data, e.g., mixed-model interpolation), (4) Failure (assumed that missing data = failure, e.g., relapse), (5) Baseline assigned (assigned a person’s baseline score if the outcome score was missing), (6) LOCF (used an imputation strategy of Last Observation Carried Forward), (7) Censored (end of FU) (data presented in a survival analysis), (8) Mean (used the mean for each person across available assessments/timepoints), (9) Other (other imputation strategy), (10) Sample FU (conducted analyses on the sample of participants that the researchers was able to follow-up), (11) Unclear (no information provided/unclear).

It was unclear whether an ITT analysis was conducted or not for 15 analyses.
The most common missing data method utilized in studies not conducting a true ITT analysis was analyzing the sample followed-up ($K=38; 27\%$), followed by censoring at the end of FU procedure ($K=25; 18\%$), assuming failure (“Failure”; $K=23; 17\%$), last observation carried forward ($K=23; 16\%$) and an unclear strategy ($K=17; 12\%$). All other missing data strategies were used $\leq10\%$ of the time. A study could be categorized as not employing an ITT strategy, but still using a missing data strategy of assuming failure or last observation carried forward if, for example, the study assumed failure for missing participants, but something less than the full randomized Ns were reported for analyses. Tables 3 and 4 display changes in ITT analyses and missing data strategies over time. No statistically significant change (although marginally significant trend) was found in use of true ITT analyses over time (Table 3). This relationship is depicted graphically with time on the x-axis, probability (of being an ITT) from generalized linear model results on the y-axis, and raw study values ($0= $not ITT, $1= $ITT) displayed as points. The 95% confidence intervals are displayed as a grey line around the probability slope.

Several statistically significant relationships between missing data strategy and time emerged, as displayed in Table 4. Specifically, censored at end of FU (for survival analyses), last observation carried forward (LOCF), and using a statistical analysis to impute/interpolate missing data (Imputed/Interpolated, e.g., mixed-model interpolation) have become more common over time, whereas analyses conducted on only the sample of participants that the researchers were able to follow-up (Sample FU) has become less common. To explore whether increasing use of certain missing data strategies over time was confounded with longitudinal methods being increasingly employed, a proxy dummy control variable...
(0=only end-of treatment assessment, 1= posttreatment and follow-up assessment(s)) was added to the analyses; the results were virtually unchanged.
Table 3. Change in true ITT analyses over time

<table>
<thead>
<tr>
<th>Estimate</th>
<th>SE</th>
<th>t-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-1.5244</td>
<td>0.6462</td>
<td>-2.3933</td>
</tr>
<tr>
<td>Year</td>
<td>0.403</td>
<td>0.02</td>
<td>1.8584</td>
</tr>
</tbody>
</table>

Note: generalized linear model with binary outcome (ITT analyses conducted=1 or not=0). *=p-value <.05)
k=165

Table 4. Change in missing data strategy over time

<table>
<thead>
<tr>
<th>Method</th>
<th>Estimate</th>
<th>SE</th>
<th>z-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fail</td>
<td>0.03</td>
<td>0.02</td>
<td>1.38</td>
<td>0.16</td>
</tr>
<tr>
<td>All FU</td>
<td>-0.10</td>
<td>0.09</td>
<td>-1.18</td>
<td>0.24</td>
</tr>
<tr>
<td>All FU (some dropout)</td>
<td>-0.09</td>
<td>0.06</td>
<td>-1.43</td>
<td>0.15</td>
</tr>
<tr>
<td>Baseline Assigned</td>
<td>0.47</td>
<td>0.36</td>
<td>1.31</td>
<td>0.19</td>
</tr>
<tr>
<td>Censored (end of FU)</td>
<td>0.09</td>
<td>0.03</td>
<td>3.19</td>
<td>&lt;0.01***</td>
</tr>
<tr>
<td>LOCF</td>
<td>0.06</td>
<td>0.03</td>
<td>2.01</td>
<td>0.045*</td>
</tr>
<tr>
<td>Grp Avg</td>
<td>0.07</td>
<td>0.12</td>
<td>0.62</td>
<td>0.54</td>
</tr>
<tr>
<td>Mean FU points</td>
<td>0.07</td>
<td>0.07</td>
<td>0.92</td>
<td>0.36</td>
</tr>
<tr>
<td>Other</td>
<td>0.05</td>
<td>0.09</td>
<td>0.55</td>
<td>0.59</td>
</tr>
<tr>
<td>Sample FU</td>
<td>-0.10</td>
<td>0.02</td>
<td>-4.40</td>
<td>&lt;0.001****</td>
</tr>
<tr>
<td><strong>Interpolation imputed</strong></td>
<td>0.33</td>
<td>0.09</td>
<td>3.83</td>
<td>&lt;0.001****</td>
</tr>
<tr>
<td>Unclear</td>
<td>0.02</td>
<td>0.02</td>
<td>0.94</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Note: generalized linear model with binary outcome.
*p-value <.05
Discussion

Across the 165 pharmacotherapy trials included in this analysis, less than half of the 74 studies reporting to have used an ITT strategy actually did so. This finding likely is due, at least in part, to a lack of a consensual definition of what constitutes an ITT analysis. In fact, the most common procedure for studies reporting, but not actually using an ITT, involved analyses on participants who completed a sufficient dose of treatment. That is, analyses were conducted on data for only those participants who completed a certain amount of treatment or who received a minimum intervention. This type of analysis is generally considered a "per protocol" approach, which contrasts to an ITT approach which includes outcome data for all participants, regardless of adherence to treatment [2].

Among the studies conducting a true ITT strategy, it was unclear what missing data strategy was used in nearly 25% of these studies. Lack of clarity in journal articles about how missing data were handled makes it difficult for readers to critically assess the study findings. A per protocol analysis answers questions of an explanatory nature, e.g., "how efficacious is this treatment for those adherent to the treatment?" In contrast, an ITT analysis provides more realistic (and usually less biased) estimates of the average treatment effects in the "real-world," as it accounts for both patient dropout and non-adherence to treatment. If findings from a per protocol analysis are incorrectly perceived as coming from an ITT analysis, treatment effects under more routine conditions of care will be overestimated. Journal editors and peer reviewers should be attentive to these issues and request that authors provide a clear description of the sample analyzed (i.e., ITT, modified ITT, per protocol) in their studies, along with details regarding how missing data were handled.
Because missing data strategies are becoming more sophisticated and are being facilitated by computer technology that is easily able to process data using complex algorithms, the diversity of missing data strategies that are employed is increasing in number. Indeed, our findings indicate that more complex imputation procedures are becoming more prevalent over time. One such imputation procedure is Multiple Imputation, [3] which involves a Bayesian estimation procedure to average outcomes across multiple imputed datasets. Missing data are then replaced with a probable value based on other available variables in the data. Presumably, the results with this approach more closely approximate the results of an ITT analysis with 100% follow-up than any other method of handling missing data that is currently available.

Conclusion

Discrepancies in reporting versus actually conducting true ITT analyses were apparent in this body of alcohol pharmacotherapy trials. Lack of clarity regarding the missing data strategy used also was common. The degree to which these problems are present in reports of trials of pharmacotherapies and psychosocial interventions for other conditions remains to be determined. In addition, consensus on a standard definition of ITT is needed, as are clearer reporting standards for analyses and the handling of missing data in reports of clinical trials.
Acknowledgments

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Ethics

No ethics approval was required for completion of this study. It aggregated previously published journal articles.
ICMJE uniform disclosure

All authors have completed the ICMJE uniform disclosure form at

www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the

submitted work; no financial relationships with any organizations that might have an interest in

the submitted work in the previous three years; no other relationships or activities that could

appear to have influenced the submitted work.
Contributorship Information

A. C. Del Re was involved in the study's design, analysis and interpretation of data, drafting the article and revising it. Natalya C. Maisel was involved in the study's design and revising the article. Janet Blodgett was involved in the study's design. John W. Finney was involved in the study's conception and design, interpretation of data, and revising it critically for important intellectual content. All authors gave final approval of the version to be published.
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**Intention-to-Treat Analyses and Missing Data Approaches in Pharmacotherapy Trials for Alcohol Use Disorders**

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Intention-to-Treat Analyses and Missing Data Approaches in Pharmacotherapy Trials for Alcohol Use Disorders

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Keywords: intention to treat, missing data strategies, research methods

Word count: 3,557, abstract: 298, references: 12, tables: 4
Abstract

Objectives: Intention-to-treat (ITT) is an analytic strategy for reducing potential bias in treatment effects arising from missing data in randomized controlled trials (RCT). Currently, no universally accepted definition of ITT exists, although many researchers consider it to require either no attrition or a strategy to handle missing data. Using the reports of a large pool of randomized controlled trials, we examined discrepancies between the types of analyses that alcohol pharmacotherapy researchers stated they used versus those they actually used. We also examined the linkage between analytic strategy (i.e., ITT or not) and how missing data on outcomes were handled (if at all), and whether data analytic and missing data strategies have changed over time.

Design: Descriptive statistics were generated for reported and actual data analytic strategy and for missing data strategy. In addition, generalized linear models determined changes over time in the use of ITT analyses and missing data strategies.

Setting: N/A

Participants: 165 RCTs of pharmacotherapy for alcohol use disorders.

Primary and secondary outcome measures: N/A

Results: Of the 165 studies, 74 reported using an ITT strategy. However, less than 40% of the studies actually conducted ITT according to the rigorous definition above. Whereas no change in the use of ITT analyses over time was found, censored (last follow-up completed) and imputed missing data strategies have increased over time, while analyses of data only for the sample actually followed have decreased.

Conclusions: Discrepancies in reporting versus actually conducting ITT analyses were found in this body of RCTs. Lack of clarity regarding the missing data strategy used was common. Consensus on a definition of ITT is important for adequate understanding of research findings.
Clearer reporting standards for analyses and the handling of missing data in pharmacotherapy trials and other intervention studies are needed.

**Strengths and Limitations**

**Strengths**
- First study to examine ITT practices in RCT pharmacotherapy trials for alcohol misuse.
- Included a large body of studies in the analyses.
- Examined changes over time in data analytic and missing data strategies across nearly 40 years of scientific research.
- Findings important for improving reporting practices in RCTs of pharmacotherapy trials for alcohol misuse.

**Limitations**
- Descriptive analyses could not determine whether there is any relationship between ITT and effect sizes.
In pharmacotherapy trials, participants typically are randomly assigned to a pharmacotherapy or a placebo (control) condition. With a sufficient sample size, randomization usually produces separate groups without systematic differences by equalizing factors within groups that may be associated with outcome (e.g., motivation, age, gender). Under ideal circumstances, the randomization process allows valid causal inferences to be made about the impact of the pharmacotherapy compared to the control condition. That is, one can be highly confident that any post-treatment differences in outcome are attributable to the impact of the medication itself and not to pre-existing differences in the characteristics of the pharmacotherapy and placebo samples. However, when the randomization process is disrupted, either through treatment dropout and/or missing data on outcomes, or when the original sample as randomized is not the same sample analyzed (analyzed N < randomized N), bias may be introduced that compromises the internal validity of results. [1–4]

The intention-to-treat (ITT) analytic strategy is one solution for eliminating or reducing bias in treatment effects arising from missing outcome data in randomized controlled trials (RCTs). [1,2] Although no universally accepted definition of ITT currently exists, the procedure nevertheless is endorsed in the Consolidated Standards for Reporting Trials (CONSORT). [5–7] One particularly succinct definition of a "true ITT" [8] analysis is "once randomized, always analyzed." [9] Under this definition, ITT involves analysis of all trial participants who were randomized, regardless of adherence to treatment protocol (e.g., dropout/withdrawal or protocol deviations). In other words, defined this way, ITT requires either no attrition or a strategy to handle missing data.

ITT has several strengths, including (1) helping to preserve the integrity of the randomization process (i.e., groups are expected to be similar except for random variation and
receipt of treatment/control condition) and (2) providing a more realistic estimate of average
treatment effects in the "real-world" as it is the norm for some patients to dropout or not adhere
to treatment. [1] Both points above address the issue of patient dropout, as analyses on only
adherent patients likely would lead to inflated estimates of treatment effects. Research has shown
that adherent patients generally do better than non-adherent patients, regardless of treatment.
[10,11] The more realistic estimates of treatment effects under conditions of routine care that are
derived from ITT analyses have particular relevance for policy makers and those interested in
hypotheses of pragmatic ("real world") importance.

A variant of the ITT approach, what Polit and Gillespie (2010) term a “modified ITT”
analysis, maintains the conditions to which people were randomly assigned and attempts to
follow-up all participants, regardless of their participation in the intervention. However, only
those successfully followed are included in the analyses. With this modified approach, however,
the balance in pre-existing characteristics across conditions sought through random assignment is
less likely to hold.

An alternative to ITT analysis, the per protocol analytic procedure (i.e., analyses based
on only “adherent” participants in randomized samples), has strengths as well and is of particular
importance for hypotheses of an explanatory nature.[12] The per protocol approach can range
from analyses in which only those research participants who began treatment are included, to
those in which only participants who received what was deemed a “sufficient dose” of treatment
are used, to those in which only participants who fully completed treatment are included [also
referred to as a ‘complete cases’ approach; 2]. Advocates of per protocol approach assert that the
analysis tests the true efficacy of the intervention when used as directed (i.e., efficacy among
those who are adherent and able to tolerate the treatment).
Because both ITT and per protocol approaches to RCT analyses have their strengths, a possible strategy is to conduct an ITT analysis, with a per protocol sensitivity analysis to “bracket” likely effects under different conditions. Nevertheless, ITT analyses are considered the "gold standard" and researchers frequently report the use of this procedure in published literature, even in the absence of a consensual definition. Discrepancies can arise, however, between the type of analyses researchers state in research reports that they conducted and what they actually did with respect to use of a “true” ITT analysis or some other procedure based on less than the full randomized sample. For example, in clinical trials in the nursing field, Polit and Gillespie (2009) found that for 10.5% of studies, researchers who stated they had used an ITT approach had actually conducted per protocol analyses.

It is unknown to what degree ITT strategies are being employed in pharmacotherapy for alcohol use disorders. One aim of this review was to determine if there are discrepancies between the types of analyses that researchers stated they used and those they actually used, based on information in reports of a large pool of randomized controlled trials of pharmacotherapy for alcohol use disorders published between 1970 to 2009. A second aim was to describe the use of different missing data strategies in studies in which true and modified ITT analyses were and were not conducted. The final aim was to determine whether the use of different data analytic approaches and certain types of missing data approaches (e.g., multiple imputation) has increased over time while the use of others has decreased.

**Methods**

**Literature Search**

As part of a larger project examining the efficacy of pharmacotherapies for alcohol use disorders and alcohol misuse, [i.e., 13] we identified relevant randomized controlled trials via
several searches of PubMed and PsycINFO conducted at different points over the past decade. Study inclusion criteria were (a) a focus on treating alcohol misuse or an alcohol use disorder; (b) participants 18 years of age or older; (c) publication between 1970 and 2009; (d) a report in the English language; and (e) random assignment of at least five participants each to medication and placebo groups. The details of inclusion/exclusion criteria can be found in Maisel et al.[12]

Searches were intermittent due to sporadic availability of funds and resources. For example, in one search we used search terms for various medications (e.g., “naltrexone”), terms for alcohol problems and use disorders and alcohol misuse (e.g., “alcohol*,” “problem drinking”) and terms for randomized controlled trials (e.g., “randomized controlled,” “clinical trial”). This search yielded 1,602 potential research reports. Based on examination of abstracts and, in some cases, full text versions of these reports, 1,184 were identified as not relevant (e.g., qualitative studies, reviews). Of the remaining articles, 215 were rejected based on not meeting our eligibility criteria (e.g., open-label trial), 138 articles met the inclusion criteria, but 65 were additional publications for studies already in the dataset (e.g., reporting secondary analyses). In addition to the database searches, we perused the reference sections from the reports of the included studies and from previously published reviews of this literature. For the present analysis, a total of 165 studies met our inclusion criteria.

Variables

Descriptive and inferential statistics were generated for two categorical variables: (1) sample analyzed and (2) missing data strategy. The categories of the “sample analyzed” variable were:

(1) Full random sample - analyses involved the total randomized N’s (with or without imputation or interpolation of missing data).
(2) Full random sample (likely) - analyses appeared to use the full randomized sample, but N’s were not reported.

(3) Random sample followed-up - attempted to follow-up all randomized participants. Regardless of amount of medication/treatment completed and conducted analyses on this sample. Note there is no overlap between categories 1 ("Full random sample") or 2 ("Full random sample (likely)") and "Random sample followed-up".

(4) Sufficient dose - analyses were conducted for only those participants who completed a specified amount of treatment or who received at least a minimum dose of treatment.

(5) Completer sample - analyses conducted for only those patients who completed the medication/treatment phase.

(6) False inclusion - after randomization, participants were found to not meet inclusion criteria and were subsequently removed from the analyses.

(7) Other - reported N’s or degrees of freedom that were less than what would be expected for the randomized N, but no explanation of the participants included or excluded from the analysis was provided.

(8) Unclear – insufficient information was provided to determine the sample analyzed.

Only analyses conducted on the Full Random Sample or Full Random Sample (likely) categories were deemed to be “true” ITT analyses, whereas the others were considered something other than ITT analyses.

The categories for the “missing data strategy” variable were as follows:

(1) No dropout – no dropout from treatment and 100% reassessed.

(2) All followed - there were drop-outs from treatment, but all participants, including treatment dropouts, were reassessed.
(3) Statistical interpolation - used a statistical analysis that interpolated missing data, e.g., mixed effects model interpolation.

(4) Failure assumed for missing data (missing = failure) - assumed that missing data reflected poor outcome, e.g., relapse.

(5) Baseline assigned - a participant’s baseline score was assigned if outcome data were missing.

(6) LOCF - used the imputation strategy of Last Observation Carried Forward.

(7) Censored – last assessment point was used in survival analyses.

(8) Mean - used the mean of the sample followed for missing data.

(9) Other – used some other imputation of missing data strategy.

(10) Sample followed - conducted analyses with data for the sample of participants that the researchers were able to follow/reassess.

(11) Unclear - no or unclear information provided.

Statistical Analyses

Descriptive statistics were generated for data analytic strategies and missing data strategies used in the 165 RCTs of pharmacotherapies for AUD and alcohol misuse. Generalized linear model analyses were conducted to determine changes in both data analytic and missing data strategy over time. In those analyses, the response variables, data analytic strategy and missing data strategy, were coded as binary (0='No', 1='Yes'), with year of publication as predictor of a 'Yes' response.

Results

As noted in Table 1, a substantial discrepancy was evident between reporting an ITT strategy versus actually conducting a “true” ITT analysis (i.e., reporting an ITT strategy when
something other than ITT was conducted). Of the 165 studies included in this review, 74 reported using an ITT strategy. However, less than half of those studies conducted a true ITT analysis ($K=29; 39\%$) according to information in study reports. Interestingly, $35\% (K=32)$ of the 91 studies whose reports made no claim of using an ITT strategy, in fact, did perform true ITT analyses.
<table>
<thead>
<tr>
<th>Reportedly Using ITT</th>
<th>Conducted True ITT</th>
<th>Sample Analyzed</th>
<th>Total Number of IIT and/or Non-ITT Approaches Used</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Full Random Sample (likely)</td>
<td>Full Random Sample FU</td>
</tr>
<tr>
<td>No (K=91)</td>
<td>(35%)</td>
<td>28 (4%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Yes (K=74)</td>
<td>(39%)</td>
<td>21 (9%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Total (K=165)</td>
<td>(37%)</td>
<td>49 (6%)</td>
<td>13 (6%)</td>
</tr>
</tbody>
</table>

Note: ITT=Full Random Sample or Full Random Sample (likely) categories; K=study, column description: (1) Full random sample (analyses involved the total randomized N’s), (2) Full random sample (likely) (appears to be using the full randomized sample, but N’s are not reported with analyses), (3) Random sample followed-up (attempted to follow-up all randomized participants regardless of amount of medication/treatment completed, and conducted analyses on this sample), (4) Sufficient dose (analyses conducted on only those participants who received a minimum amount of medication/treatment), (5) Completor sample (analyses conducted on only those patients who completed the medication/treatment phase), (6) False inclusion (after randomization, participant is found to not meet inclusion criteria and is subsequently removed from the analyses), (7) Other (analyses report N’s or degrees of freedom that are less than what would be expected for the randomized N, but no explanation on the participants included or excluded from the analysis is provided), and (8) Unclear (insufficient information to determine the sample analyzed). Only categories (1) Full random sample and (2) Full random sample (likely) are considered a “true” ITT strategy, whereas the others are considered something other than ITT.
Regarding the specific data analytic strategy used, the values in each row of Table 1 do not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming failure for dichotomous outcomes AND also used a complete cases approach for continuous outcomes). In such instances, we coded "Reported Using ITT" as "Yes" if the study mentioned using an ITT strategy and coded it as "No" otherwise (i.e., no mention of using an ITT strategy).

The most common approach utilized in studies reporting the use of an ITT strategy, other than use of a true ITT (K=29; 39%), involved analyses of data for participants who completed a “sufficient dose” of the medication/treatment (K=40; 39%). All other strategies were utilized <10% of the time. The most common analytic method used in studies not mentioning an ITT strategy was actually a true ITT analysis (K=32; 29%), followed by analyses of data from completer samples (K=31; 28%), analyses for participants who completed a “sufficient dose” of medication/treatment (K=19; 17%), and indeterminable strategies (i.e., Unclear; K=16; 14%).

Table 2 reports the descriptive information on the missing data strategies employed in the studies using and not using a true ITT approach. Similar to Table 1, the values in each row of Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due to 42 studies utilizing multiple missing data strategies. The most common missing data strategy utilized in studies employing an ITT approach was either unclear (K=24; 23%) or involved censoring data at the end of FU procedure in survival analyses (K=23; 22%). A study could be categorized as employing an ITT strategy, but having an unclear missing data strategy if, for example, the study reported the full randomized Ns from analyses, but it was unclear what particular missing data strategy was utilized. The next most frequently used strategies were
assuming missing equals relapse or some other poor outcome ("Failure"; $K=14$; 13%) and using a statistical interpolation strategy ($K=14$; 13%), such as a mixed effects model. All other missing data strategies were utilized $\leq 10\%$ of the time, except the last observation carried forward (LOCF) procedure that was used in ($K=12$) 11% of the studies.
Table 2.

<table>
<thead>
<tr>
<th>Conducted True ITT</th>
<th>Missing Data Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Tx or FU Dropout</td>
<td>No Tx or FU Dropout</td>
</tr>
<tr>
<td>All FU (some tx dropout)</td>
<td>All FU (some tx dropout)</td>
</tr>
<tr>
<td>Interpolation</td>
<td>Interpolation</td>
</tr>
<tr>
<td>Missing Failure</td>
<td>Missing Failure</td>
</tr>
<tr>
<td>Baseline Assigned</td>
<td>Baseline Assigned</td>
</tr>
<tr>
<td>LOC F</td>
<td>LOC F</td>
</tr>
<tr>
<td>Censored (end of FU) Survival Analysis</td>
<td>Censored (end of FU) Survival Analysis</td>
</tr>
<tr>
<td>Mean Substituted</td>
<td>Mean Substituted</td>
</tr>
<tr>
<td>Other Sample FU</td>
<td>Other Sample FU</td>
</tr>
<tr>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Total Number of ITT and/or Non-ITT Approaches Used</td>
<td>Total Number of ITT and/or Non-ITT Approaches Used</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No (K=104)</th>
<th>Yes (K=61)</th>
<th>Total (K=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>(4%)</td>
<td>(13%)</td>
<td>(07%)</td>
</tr>
<tr>
<td>23</td>
<td>14</td>
<td>37</td>
</tr>
<tr>
<td>(17%)</td>
<td>(13%)</td>
<td>(16%)</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>(1%)</td>
<td>(1%)</td>
<td>(&gt;1%)</td>
</tr>
<tr>
<td>22</td>
<td>12</td>
<td>34</td>
</tr>
<tr>
<td>(16%)</td>
<td>(11%)</td>
<td>(13%)</td>
</tr>
<tr>
<td>25</td>
<td>23</td>
<td>48</td>
</tr>
<tr>
<td>(18%)</td>
<td>(22%)</td>
<td>(19%)</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>(2%)</td>
<td>(2%)</td>
<td>(2%)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>(1%)</td>
<td>(1%)</td>
<td>(1%)</td>
</tr>
<tr>
<td>38</td>
<td>11</td>
<td>49</td>
</tr>
<tr>
<td>(27%)</td>
<td>(10%)</td>
<td>(19%)</td>
</tr>
<tr>
<td>17</td>
<td>24</td>
<td>41</td>
</tr>
<tr>
<td>(12%)</td>
<td>(23%)</td>
<td>(16%)</td>
</tr>
<tr>
<td>139</td>
<td>105</td>
<td>259*</td>
</tr>
</tbody>
</table>

Note. Column description: (1) No dropout, (2) Followed-up (some dropout) (there were drop-outs from treatment, but all participants, including dropouts were followed-up), (3) Interpolation (used a statistical analysis that interpolated missing data, e.g., mixed effects model interpolation), (4) Failure (assumed that missing data = failure, e.g., relapse), (5) Baseline assigned (assigned a person’s baseline score if the outcome score was missing), (6) LOCF (used an imputation strategy of Last Observation Carried Forward), (7) Censored (end of FU) (data presented in a survival analysis), (8) Mean (used the mean for each person across available assessments/timepoints), (9) Other (other imputation strategy), (10) Sample FU (conducted analyses on the sample of participants that the researchers was able to follow-up), (11) Unclear (no information provided/unclear).
The most common missing data method utilized in studies not conducting a true ITT analysis was analyzing the sample followed-up ($K=38; 27\%$), followed by censoring at the end of FU procedure ($K=25; 18\%$), assuming failure (“Failure”; $K=23; 17\%$), last observation carried forward ($K=23; 16\%$) and an unclear strategy ($K=17; 12\%$). All other missing data strategies were used $\leq 10\%$ of the time. A study could be categorized as not employing an ITT strategy, but still using a missing data strategy of assuming failure or last observation carried forward if, for example, the study assumed failure for missing participants, but something less than the full randomized $Ns$ were reported for analyses. Tables 3 and 4 display changes in ITT analyses and missing data strategies over time. No statistically significant change (although marginally significant trend) was found in use of true ITT analyses over time (Table 3). This relationship is depicted graphically with time on the $x$-axis, probability (of being an ITT) from generalized linear model results on the $y$-axis, and raw study values ($0=$ not ITT, $1=$ITT) displayed as points. The 95% confidence intervals are displayed as a grey line around the probability slope.

Several statistically significant relationships between missing data strategy and time emerged, as displayed in Table 4. Specifically, censored at end of FU (for survival analyses), last observation carried forward (LOCF), and using a statistical analysis to interpolate missing data (Interpolation, e.g., mixed effects model interpolation) have become more common over time, whereas analyses conducted on only the samples of participants that the researchers were able to follow-up (Sample FU) has become less common. To explore whether increasing use of certain missing data strategies over time was confounded with longitudinal methods being increasingly employed, a proxy dummy control variable ($0=$only end-of treatment assessment, $1=$
posttreatment and follow-up assessment(s)) was added to the analyses; the results were virtually unchanged.
### Table 3. Change in true ITT analyses over time

<table>
<thead>
<tr>
<th>Estimate</th>
<th>SE</th>
<th>t-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-1.52</td>
<td>0.64</td>
<td>-2.39</td>
</tr>
<tr>
<td>Year</td>
<td>0.04</td>
<td>0.02</td>
<td>1.85</td>
</tr>
</tbody>
</table>

Note: generalized linear model with binary outcome  
(ITT analyses conducted=1 or not=0). *=p-value <.05  
k=165

### Table 4. Change in missing data strategy over time

<table>
<thead>
<tr>
<th>Estimate</th>
<th>SE</th>
<th>z-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fail</td>
<td>0.03</td>
<td>0.02</td>
<td>1.38</td>
</tr>
<tr>
<td>All FU</td>
<td>-0.10</td>
<td>0.09</td>
<td>-1.18</td>
</tr>
<tr>
<td>All FU (some dropout)</td>
<td>-0.09</td>
<td>0.06</td>
<td>-1.43</td>
</tr>
<tr>
<td>Baseline Assigned</td>
<td>0.47</td>
<td>0.36</td>
<td>1.31</td>
</tr>
<tr>
<td>Censored (end of FU)</td>
<td>0.09</td>
<td>0.03</td>
<td>3.19</td>
</tr>
<tr>
<td>LOCF</td>
<td>0.06</td>
<td>0.03</td>
<td>2.01</td>
</tr>
<tr>
<td>Grp Avg</td>
<td>0.07</td>
<td>0.12</td>
<td>0.62</td>
</tr>
<tr>
<td>Mean FU points</td>
<td>0.07</td>
<td>0.07</td>
<td>0.92</td>
</tr>
<tr>
<td>Other</td>
<td>0.05</td>
<td>0.09</td>
<td>0.55</td>
</tr>
<tr>
<td>Sample FU</td>
<td>-0.10</td>
<td>0.02</td>
<td>-4.40</td>
</tr>
<tr>
<td>Interpolation</td>
<td>0.33</td>
<td>0.09</td>
<td>3.83</td>
</tr>
<tr>
<td>Unclear</td>
<td>0.02</td>
<td>0.02</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Note: generalized linear model with binary outcome.  
*=p-value <.05
Discussion

Across the 165 pharmacotherapy trials included in this analysis, less than half of the 74 studies reporting to have used an ITT strategy actually did so. This finding likely is due, at least in part, to a lack of a consensual definition of what constitutes an ITT analysis. In fact, the most common procedure for studies reporting, but not actually using an ITT, involved analyses on participants who completed a sufficient dose of treatment. That is, analyses were conducted on data for only those participants who completed a certain amount of treatment or who received a minimum intervention. This type of analysis is generally considered a "per protocol" approach, which contrasts to an ITT approach which includes outcome data for all participants, regardless of adherence to treatment [2].

Among the studies conducting a true ITT strategy, it was unclear what missing data strategy was used in nearly 25% of these studies. Lack of clarity in journal articles about how missing data were handled makes it difficult for readers to critically assess the study findings. A per protocol analysis answers questions of an explanatory nature, e.g., "how efficacious is this treatment for those adherent to the treatment?" In contrast, an ITT analysis provides more realistic (and usually less biased) estimates of the average treatment effects in the "real-world," as it accounts for both patient dropout and non-adherence to treatment. If findings from a per protocol analysis are incorrectly perceived as coming from an ITT analysis, treatment effects under more routine conditions of care will be overestimated. Journal editors and peer reviewers should be attentive to these issues and request that authors provide a clear description of the sample analyzed (i.e., ITT, modified ITT, per protocol) in their studies, along with details regarding how missing data were handled.
Because missing data strategies are becoming more sophisticated and are being facilitated by computer technology that is easily able to process data using complex algorithms, the diversity of missing data strategies that are employed is increasing. Indeed, our findings indicate that more complex imputation or interpolation procedures are becoming more prevalent over time. One such imputation procedure is Multiple Imputation, [3] which involves a Bayesian estimation procedure to average outcomes across multiple imputed datasets. Missing data are then replaced with a probable value based on other available variables in the data. Presumably, the results with this approach more closely approximate the results of an ITT analysis with 100% follow-up than any other method of handling missing data that is currently available.

Conclusion

Discrepancies in reporting versus actually conducting true ITT analyses were apparent in this body of alcohol pharmacotherapy trials. Lack of clarity regarding the missing data strategy used also was common. The degree to which these problems are present in reports of trials of pharmacotherapies and psychosocial interventions for other conditions remains to be determined. In addition, consensus on a standard definition of ITT is needed, as are clearer reporting standards for analyses and the handling of missing data in reports of clinical trials.
Acknowledgments

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Ethics

No ethics approval was required for completion of this study. It aggregated previously published journal articles.

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Competing interest

There are no competing interests.

Data sharing

No additional data available.

ICMJE uniform disclosure

All authors have completed the ICMJE uniform disclosure form at

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the submitted work in the previous three years; no other relationships or activities that could
appear to have influenced the submitted work.

**Contributorship Information**

A. C. Del Re was involved in the study's design, analysis and interpretation of data, drafting the article and revising it. Natalya C. Maisel was involved in the study's design and revising the article. Janet Blodgett was involved in the study's design. John W. Finney was involved in the study's conception and design, interpretation of data, and revising it critically for important intellectual content. All authors gave final approval of the version to be published.

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Intention-to-Treat Analyses and Missing Data Approaches in Pharmacotherapy Trials for Alcohol Use Disorders

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Abstract

Objectives: Intention-to-treat (ITT) is an analytic strategy for reducing potential bias in treatment effects arising from missing data in randomized controlled trials (RCT). Currently, no universally accepted definition of ITT exists, although many researchers consider it to require either no attrition or some imputation procedure to account for handle missing outcome data in analyses. Using the reports of a large pool of randomized controlled trials, we examined discrepancies between the types of analyses that alcohol pharmacotherapy researchers stated they used versus those they actually used. We also examined the linkage between analytic strategy (i.e., ITT or not) and how missing data on outcomes were handled (if at all), and whether data analytic and missing data strategies have changed over time.

Design: Descriptive statistics were generated for reported and actual data analytic strategy and for missing data strategy. In addition, generalized linear models determined changes over time in the use of ITT analyses and missing data strategies.

Setting: N/A

Participants: 165 RCTs of pharmacotherapy for alcohol use disorders.

Primary and secondary outcome measures: N/A

Results: Of the 165 studies, 74 reported using an ITT strategy. However, less than 40% of the studies actually conducted ITT according to the rigorous definition above. Whereas no change in the use of ITT analyses over time was found, censored (last follow-up completed) and imputed missing data strategies have increased over time, while analyses of data only for the sample actually followed have decreased.

Conclusions: Discrepancies in reporting versus actually conducting ITT analyses were found in this body of RCTs. Lack of clarity regarding the missing data strategy used was common. Consensus on a definition of ITT is important for adequate understanding of research findings.
Clearer reporting standards for analyses and the handling of missing data in pharmacotherapy trials and other intervention studies are needed.

**Strengths**
- Examined a large body of RCT pharmacotherapy trials for alcohol misuse.
- Findings important for improving reporting practices in RCTs of pharmacotherapy trials for alcohol misuse.

**Limitations**
- Descriptive analyses could not determine whether there is any relationship between ITT and effect sizes.
In pharmacotherapy trials, participants typically are randomly assigned to a pharmacotherapy or a placebo (control) condition. With a sufficient sample size, randomization usually produces separate groups without systematic differences by equalizing factors within groups that may be associated with outcome (e.g., motivation, age, gender). Under ideal circumstances, the randomization process allows valid causal inferences to be made about the impact of the pharmacotherapy compared to the control condition. That is, one can be highly confident that any post-treatment differences in outcome are attributable to the impact of the medication itself and not to pre-existing differences in the characteristics of the pharmacotherapy and placebo samples. However, when the randomization process is disrupted, either through treatment dropout and/or missing data on outcomes, or when the original sample as randomized is not the same sample analyzed (analyzed N < randomized N), bias may be introduced that compromises the internal validity of results. [1–4]

The intention-to-treat (ITT) analytic strategy is one solution for eliminating or reducing bias in treatment effects arising from missing outcome data in randomized controlled trials (RCTs). [1,2] Although no universally accepted definition of ITT currently exists, the procedure nevertheless is endorsed in the Consolidated Standards for Reporting Trials (CONSORT). [5–7] One particularly succinct definition of a "true ITT" [8] analysis is "once randomized, always analyzed." [9] Under this definition, ITT involves analysis of all trial participants who were randomized, regardless of adherence to treatment protocol (e.g., dropout/withdrawal or protocol deviations). In other words, defined this way, ITT requires either no attrition or some imputation strategy to account for any missing data.

ITT has several strengths, including (1) helping to preserve the integrity of the randomization process (i.e., groups are expected to be similar except for random variation and...
receipt of treatment/control condition) and (2) providing a more realistic estimate of average
treatment effects in the "real-world" as it is the norm for some patients to dropout or not adhere
to treatment. [1] Both points above address the issue of patient dropout, as analyses on only
adherent patients likely would lead to inflated estimates of treatment effects. Research has shown
that adherent patients generally do better than non-adherent patients, regardless of treatment.
[10,11] The more realistic estimates of treatment effects under conditions of routine care that are
derived from ITT analyses have particular relevance for policy makers and those interested in
hypotheses of pragmatic ("real world") importance.

A variant of the ITT approach, what Polit and Gillespie (2010) term a “modified ITT”
analysis, maintains the conditions to which people were randomly assigned and attempts to
follow-up all participants, regardless of their participation in the intervention. However, only
those successfully followed are included in the analyses. With this modified approach, however,
the balance in pre-existing characteristics across conditions sought through random assignment is
less likely to hold.

An alternative to ITT analysis, the per protocol analytic procedure (i.e., analyses based
on only “adherent” participants in randomized samples), has strengths as well and is of particular
importance for hypotheses of an explanatory nature. [12] The per protocol approach can range
from analyses in which only those research participants who began treatment are included, to
those in which only participants who received what was deemed a “sufficient dose” of treatment
are used, to those in which only participants who fully completed treatment are included also
referred to as a ‘complete cases’ approach [also referred to as a ‘complete cases’ approach; 2].
Advocates of per protocol approach assert that the analysis tests the true efficacy of the
intervention when used as directed (i.e., efficacy among those who are adherent and able
to tolerate the treatment).

Because both ITT and per protocol approaches to RCT analyses have their strengths, a
possible strategy is to conduct an ITT analysis, with a per protocol sensitivity analysis to
“bracket” likely effects under different conditions. Nevertheless, ITT analyses are considered
the "gold standard" and researchers frequently report the use of this procedure in published
literature, even in the absence of a consensual definition. Discrepancies can arise, however,
between the type of analyses researchers state in research reports that they conducted and what
they actually did with respect to use of a “true” ITT analysis or some other procedure based on
less than the full randomized sample. For example, in clinical trials in the nursing field, Polit
and Gillespie (2009) found that for 10.5% of studies, researchers who stated they had used an
ITT approach had actually conducted per protocol analyses.

It is unknown to what degree ITT strategies are being employed in pharmacotherapy for
alcohol use disorders. One aim of this review was to determine if there are discrepancies between
the types of analyses that researchers stated they used and those they actually used, based on
information in reports of a large pool of randomized controlled trials of pharmacotherapy for
alcohol use disorders published between 1970 to 2009. A second aim was to describe the use of
different missing data strategies in studies in which true and modified ITT analyses were and
were not conducted. The final aim was to determine whether the use of different data analytic
approaches and certain types of missing data approaches (e.g., multiple imputation) has
increased over time while the use of others has decreased.

Methods

Literature Search
As part of a larger project examining the efficacy of pharmacotherapies for alcohol use disorders and alcohol misuse, [i.e., 13] we identified relevant randomized controlled trials via several searches of PubMed and PsycINFO conducted at different points over the past decade. Study inclusion criteria were (a) a focus on treating alcohol misuse or an alcohol use disorder; (b) participants 18 years of age or older; (c) publication between 1970 and 2009; (d) a report in the English language; and (e) random assignment of at least five participants each to medication and placebo groups. The details of inclusion/exclusion criteria can be found in Maisel et al.[12] Searches were intermittent due to sporadic availability of funds and resources. For example, in one search we used search terms for various medications (e.g., “naltrexone”), terms for alcohol problems and use disorders and alcohol misuse (e.g., “alcohol*,” “problem drinking”) and terms for randomized controlled trials (e.g., “randomized controlled,” “clinical trial”). This search yielded 1,602 potential research reports. Based on examination of abstracts and, in some cases, full text versions of these reports, 1,184 were identified as not relevant (e.g., qualitative studies, reviews). Of the remaining articles, 215 were rejected based on not meeting our eligibility criteria (e.g., open-label trial), 138 articles met the inclusion criteria, but 65 were additional publications for studies already in the dataset (e.g., reporting secondary analyses). In addition to the database searches, we pursued the reference sections from the reports of the included studies and from previously published reviews of this literature. For the present analysis, a total of 165 studies met our inclusion criteria.

Variables

Descriptive and inferential statistics were generated for two categorical variables: (1) sample analyzed and (2) missing data strategy. The categories of the “sample analyzed” variable were:
1. Full random sample - analyses involved the total randomized N’s (with or without imputation or interpolation of missing data).

2. Full random sample (likely) - analyses appeared to use the full randomized sample, but N’s were not reported.

3. Random sample followed-up - attempted to follow-up all randomized participants regardless of amount of medication/treatment completed and conducted analyses on this sample. Note there is no overlap between categories 1 ("Full random sample") or 2 ("Full random sample (likely)") and "Random sample followed-up".

4. Sufficient dose - analyses were conducted for only those participants who completed a specified amount of treatment or who received at least a minimum dose of treatment.

5. Completer sample - analyses conducted for only those patients who completed the medication/treatment phase.

6. False inclusion - after randomization, participants were found to not meet inclusion criteria and were subsequently removed from the analyses.

7. Other - reported N’s or degrees of freedom that were less than what would be expected for the randomized N, but no explanation of the participants included or excluded from the analysis was provided.

8. Unclear – insufficient information was provided to determine the sample analyzed.

Only analyses conducted on the Full Random Sample or Full Random Sample (likely) categories were deemed to be “true” ITT analyses, whereas the others were considered something other than ITT analyses.

The categories for the “missing data strategy” variable were as follows:

(1) No dropout – no dropout from treatment and 100% reassessed.
(2) All followed - there were drop-outs from treatment, but all participants, including treatment dropouts, were reassessed.

(3) Statistical imputation or interpolation - used a statistical analysis that imputed or interpolated missing data, e.g., mixed-effects model interpolation.

(4) Failure assumed for missing data (missing = failure) - assumed that missing data reflected poor outcome, e.g., relapse.

(5) Baseline assigned - a participant’s baseline score was assigned if outcome data were missing.

(6) LOCF - used the imputation strategy of Last Observation Carried Forward.

(7) Censored – last assessment point was used in survival analyses.

(8) Mean - used the mean of the sample followed for missing data.

(9) Other – used some other imputation of missing data strategy.

(10) Sample followed - conducted analyses with data for the sample of participants that the researchers were able to follow/reassess.

(11) Unclear - no or unclear information provided.

Statistical Analyses

Descriptive statistics were generated for data analytic strategies and missing data strategies used in the 165 RCTs of pharmacotherapies for AUD and alcohol misuse. Generalized linear model analyses were conducted to determine changes in both data analytic and missing data strategy over time. In those analyses, the response variables, data analytic strategy and missing data strategy, were coded as binary (0='No', 1='Yes'), with year of publication as predictor of a 'Yes' response.

Results
As noted in Table 1, a substantial discrepancy was evident between reporting an ITT strategy versus actually conducting a “true” ITT analysis (i.e., reporting an ITT strategy when something other than ITT was conducted). Of the 165 studies included in this review, 74 reported using an ITT strategy. However, less than half of those studies conducted a true ITT analysis ($K=29$; 39%) according to information in study reports. Interestingly, 35% ($K=32$) of the 91 studies whose reports made no claim of using an ITT strategy, in fact, did perform true ITT analyses.
Table 1.

<table>
<thead>
<tr>
<th>Reported Using ITT</th>
<th>Conducted True ITT*</th>
<th>Sample Analyzed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full Random Sample</td>
<td>Full Random Sample (likely)</td>
</tr>
<tr>
<td>No (K=91)</td>
<td>32</td>
<td>28 (25%)</td>
</tr>
<tr>
<td>Yes (K=74)</td>
<td>29</td>
<td>21 (21%)</td>
</tr>
<tr>
<td>Total (K=165)</td>
<td>61</td>
<td>49 (23%)</td>
</tr>
</tbody>
</table>

Note: *ITT=Full Random Sample or Full Random Sample (likely) categories; K=study, column description: (1) Full random sample (analyses involved the total randomized N’s), (2) Full random sample (likely) (appears to be using the full randomized sample, but N’s are not reported with analyses), (3) Random sample followed-up (attempted to follow-up all randomized participants regardless of amount of medication/treatment completed, and conducted analyses on this sample), (4) Sufficient dose (analyses conducted on only those participants who received a minimum amount of medication/treatment), (5) Completer sample (analyses conducted on only those patients who completed the medication/treatment phase), (6) False inclusion (after randomization, participant is found to not meet inclusion criteria and is subsequently removed from the analyses), (7) Other (analyses report N’s or degrees of freedom that are less than what would be expected for the randomized N, but no explanation on the participants included or excluded from the analysis is provided), and (8) Unclear (insufficient information to determine the sample analyzed). Only categories (1) Full random sample and (2) Full random sample (likely) are considered a “true” ITT strategy, whereas the others are considered something other than ITT.
Regarding the specific data analytic strategy used, the values in each row of Table 1 do not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming failure for dichotomous outcomes AND also used a complete cases approach for continuous outcomes). In such instances, we coded "Reported Using ITT" as "Yes" if the study mentioned using an ITT strategy and coded it as "No" otherwise (i.e., no mention of using an ITT strategy).

The most common approach utilized in studies reporting the use of an ITT strategy, other than use of a true ITT (K=29; 39%), involved analyses of data for participants who completed a "sufficient dose" of the medication/treatment (K=40; 39%). All other strategies were utilized <10% of the time. The most common analytic method used in studies not mentioning an ITT strategy was actually a true ITT analysis (K=32; 29%), followed by analyses of data from completer samples (K=31; 28%), analyses for participants who completed a "sufficient dose" of medication/treatment (K=19; 17%), and indeterminable strategies (i.e., Unclear; K=16; 14%).

Table 2 reports the descriptive information on the missing data strategies employed in the studies using and not using a true ITT approach. Similar to Table 1, the values in each row of Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due to 42 studies utilizing multiple missing data strategies. The most common missing data strategy utilized in studies employing an ITT approach was either unclear (K=24; 23%) or involved censoring data at the end of FU procedure in survival analyses (K=23; 22%). A study could be categorized as employing an ITT strategy, but having an unclear missing data strategy if, for example, the study reported the full randomized Ns from analyses, but it was unclear what particular missing data strategy was utilized. The next most frequently used strategies were
assuming missing equals relapse or some other poor outcome ("Failure"; \( K=14; 13\% \)) and using a statistical imputation or interpolation strategy (\( K=14; 13\% \)), such as a mixed effects model. All other missing data strategies were utilized \( \leq 10\% \) of the time, except the last observation carried forward (LOCF) procedure that was used in (\( K=12 \)) 11\% of the studies.
Table 2.

<table>
<thead>
<tr>
<th>Conducted True ITT</th>
<th>Missing Data Strategy</th>
<th>Total Number of ITT and/or Non-ITT Approaches Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Tx or FU Dropout</td>
<td>No FU (some tx dropout)</td>
<td>Imputation or Interpolation</td>
</tr>
<tr>
<td>No (K=104)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yes (K=61)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total (K=165)</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Note. Column description: (1) No dropout, (2) Followed-up (some dropout) (there were drop-outs from treatment, but all participants, including dropouts were followed-up), (3) Imputation or Interpolation (used a statistical analysis that interpolated missing data, e.g., mixed-effects model interpolation), (4) Failure (assumed that missing data = failure, e.g., relapse), (5) Baseline assigned (assigned a person’s baseline score if the outcome score was missing), (6) LOCF (used an imputation strategy of Last Observation Carried Forward), (7) Censored (end of FU) (data presented in a survival analysis), (8) Mean (used the mean for each person across available assessments/timepoints), (9) Other (other imputation strategy), (10) Sample FU (conducted analyses on the sample of participants that the researchers was able to follow-up), (11) Unclear (no information provided/unclear).
The most common missing data method utilized in studies not conducting a true ITT analysis was analyzing the sample followed-up (K=38; 27%), followed by censoring at the end of FU procedure (K=25; 18%), assuming failure (“Failure”; K=23; 17%), last observation carried forward (K=23; 16%) and an unclear strategy (K=17; 12%). All other missing data strategies were used ≤10% of the time. A study could be categorized as not employing an ITT strategy, but still using a missing data strategy of assuming failure or last observation carried forward if, for example, the study assumed failure for missing participants, but something less than the full randomized Ns were reported for analyses. Tables 3 and 4 display changes in ITT analyses and missing data strategies over time. No statistically significant change (although marginally significant trend) was found in use of true ITT analyses over time (Table 3). This relationship is depicted graphically with time on the x-axis, probability (of being an ITT) from generalized linear model results on the y-axis, and raw study values (0= not ITT, 1=ITT) displayed as points.

The 95% confidence intervals are displayed as a grey line around the probability slope.

Several statistically significant relationships between missing data strategy and time emerged, as displayed in Table 4. Specifically, censored at end of FU (for survival analyses), last observation carried forward (LOCF), and using a statistical analysis to impute/interpolate missing data (imputed/interpolated/Interpolation, e.g., mixed effects model interpolation) have become more common over time, whereas analyses conducted on only the samples of participants that the researchers were able to follow-up (Sample FU) has become less common. To explore whether increasing use of certain missing data strategies over time was confounded with longitudinal methods being increasingly employed, a proxy dummy control variable
(0=only end-of treatment assessment, 1= posttreatment and follow-up assessment(s)) was added to the analyses; the results were virtually unchanged.
Table 3. Change in true ITT analyses over time

<table>
<thead>
<tr>
<th>Estimate</th>
<th>SE</th>
<th>t-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-1.52</td>
<td>0.64</td>
<td>-2.39</td>
</tr>
<tr>
<td>Year</td>
<td>0.04</td>
<td>0.02</td>
<td>1.85</td>
</tr>
</tbody>
</table>

Note: generalized linear model with binary outcome
(ITT analyses conducted=1 or not=0). *=p-value <.05
k=165

Table 4. Change in missing data strategy over time

<table>
<thead>
<tr>
<th>Estimate</th>
<th>SE</th>
<th>z-value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fail</td>
<td>0.03</td>
<td>0.02</td>
<td>1.38</td>
</tr>
<tr>
<td>All FU</td>
<td>-0.10</td>
<td>0.09</td>
<td>-1.18</td>
</tr>
<tr>
<td>All FU (some dropout)</td>
<td>-0.09</td>
<td>0.06</td>
<td>-1.43</td>
</tr>
<tr>
<td>Baseline Assigned</td>
<td>0.47</td>
<td>0.36</td>
<td>1.31</td>
</tr>
<tr>
<td>Censored (end of FU)</td>
<td>0.09</td>
<td>0.03</td>
<td>3.19</td>
</tr>
<tr>
<td>LOCF</td>
<td>0.06</td>
<td>0.03</td>
<td>2.01</td>
</tr>
<tr>
<td>Grp Avg</td>
<td>0.07</td>
<td>0.12</td>
<td>0.62</td>
</tr>
<tr>
<td>Mean FU points</td>
<td>0.07</td>
<td>0.07</td>
<td>0.92</td>
</tr>
<tr>
<td>Other</td>
<td>0.05</td>
<td>0.09</td>
<td>0.55</td>
</tr>
<tr>
<td>Sample FU</td>
<td>-0.10</td>
<td>0.02</td>
<td>-4.40</td>
</tr>
<tr>
<td><strong>Imputation or Interpolation</strong></td>
<td>0.33</td>
<td>0.09</td>
<td>3.83</td>
</tr>
<tr>
<td>Unclear</td>
<td>0.02</td>
<td>0.02</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Note: generalized linear model with binary outcome.
*=p-value <.05
Discussion

Across the 165 pharmacotherapy trials included in this analysis, less than half of the 74 studies reporting to have used an ITT strategy actually did so. This finding likely is due, at least in part, to a lack of a consensual definition of what constitutes an ITT analysis. In fact, the most common procedure for studies reporting, but not actually using an ITT, involved analyses on participants who completed a sufficient dose of treatment. That is, analyses were conducted on data for only those participants who completed a certain amount of treatment or who received a minimum intervention. This type of analysis is generally considered a "per protocol" approach, which contrasts to an ITT approach which includes outcome data for all participants, regardless of adherence to treatment [2].

Among the studies conducting a true ITT strategy, it was unclear what missing data strategy was used in nearly 25% of these studies. Lack of clarity in journal articles about how missing data were handled makes it difficult for readers to critically assess the study findings. A per protocol analysis answers questions of an explanatory nature, e.g., "how efficacious is this treatment for those adherent to the treatment?" In contrast, an ITT analysis provides more realistic (and usually less biased) estimates of the average treatment effects in the "real-world," as it accounts for both patient dropout and non-adherence to treatment. If findings from a per protocol analysis are incorrectly perceived as coming from an ITT analysis, treatment effects under more routine conditions of care will be overestimated. Journal editors and peer reviewers should be attentive to these issues and request that authors provide a clear description of the sample analyzed (i.e., ITT, modified ITT, per protocol) in their studies, along with details regarding how missing data were handled.
Because missing data strategies are becoming more sophisticated and are being facilitated by computer technology that is easily able to process data using complex algorithms, the diversity of missing data strategies that are employed is increasing. Indeed, our findings indicate that more complex imputation or interpolation procedures are becoming more prevalent over time. One such imputation procedure is Multiple Imputation, [3] which involves a Bayesian estimation procedure to average outcomes across multiple imputed datasets. Missing data are then replaced with a probable value based on other available variables in the data. Presumably, the results with this approach more closely approximate the results of an ITT analysis with 100% follow-up than any other method of handling missing data that is currently available.

Conclusion

Discrepancies in reporting versus actually conducting true ITT analyses were apparent in this body of alcohol pharmacotherapy trials. Lack of clarity regarding the missing data strategy used also was common. The degree to which these problems are present in reports of trials of pharmacotherapies and psychosocial interventions for other conditions remains to be determined. In addition, consensus on a standard definition of ITT is needed, as are clearer reporting standards for analyses and the handling of missing data in reports of clinical trials.
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Ethics

No ethics approval was required for completion of this study. It aggregated previously published journal articles.
ICMJE uniform disclosure

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.
Contributorship Information

A. C. Del Re was involved in the study's design, analysis and interpretation of data, drafting the article and revising it. Natalya C. Maisel was involved in the study's design and revising the article. Janet Blodgett was involved in the study's design. John W. Finney was involved in the study's conception and design, interpretation of data, and revising it critically for important intellectual content. All authors gave final approval of the version to be published.
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