



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

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6 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.

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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.

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4 In pharmacotherapy trials, participants typically are randomly assigned to a
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6 pharmacotherapy or a placebo (control) condition. With a sufficient sample size, randomization
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8 usually produces separate groups *without* systematic differences by equalizing factors within
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10 groups that may be associated with outcome (e.g., motivation, age, gender). Under ideal
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12 circumstances, the randomization process allows valid causal inferences to be made about the
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14 impact of the pharmacotherapy compared to the control condition. That is, one can be highly
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16 confident that any post-treatment differences in outcome are attributable to the impact of the
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18 medication itself and not to pre-existing differences between the characteristics of the
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20 pharmacotherapy and placebo samples. However, when the randomization process is disrupted,
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22 either through treatment dropout and/or missing data on outcomes, or when the original sample
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24 as randomized is not the same sample analyzed (analyzed N < randomized N), bias may be
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26 introduced that compromises the internal validity of results.¹⁻⁴
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32 The intention-to-treat (ITT) analytic strategy is one solution for eliminating or reducing
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34 bias in treatment effects arising from missing outcome data in randomized controlled trials
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36 (RCTs).^{1,2} Although no universally accepted definition of ITT currently exists, the procedure
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38 nevertheless is endorsed in the Consolidated Standards for Reporting Trials (CONSORT).⁵⁻⁷
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40 One particularly succinct definition of a "true ITT"⁸ analysis is "once randomized, always
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42 analyzed" (Schulz and Grimes, 2002, p. 781). Under this definition, ITT involves analysis of *all*
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44 trial participants who were randomized, regardless of adherence to treatment protocol (e.g.,
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46 dropout/withdrawal or protocol deviations). In other words, defined this way, ITT requires either
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48 no attrition or some imputation procedure to account for any missing data.
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53 ITT has several strengths, including (1) helping to preserve the integrity of the
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55 randomization process (i.e., groups are expected to be similar except for random variation and
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3 receipt of treatment/control condition) and (2) providing a more realistic estimate of average
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5 treatment effects in the "real-world" as it is the norm for some patients to dropout or not adhere
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7 to treatment.¹ Both points above address the issue of patient dropout, as analyses on only
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9 adherent patients likely would lead to inflated estimates of treatment effects. Research has shown
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11 that adherent patients generally do better than non-adherent patients, regardless of treatment.^{10 11}
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14 The more realistic estimates of treatment effects under conditions of routine care that are derived
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16 from ITT analyses have particular relevance for policy makers and those interested in hypotheses
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18 of pragmatic ("real world") importance.
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23 A variant of the ITT approach, what it termed a "modified ITT" analysis,⁸ maintains the
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25 conditions to which people were randomly assigned and attempts to follow-up all participants,
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27 regardless of their participation in the intervention. However, only those successfully followed
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29 are included in the analyses. With this modified approach, however, the balance in pre-existing
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31 characteristics across conditions sought through random assignment is less likely to hold.
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35 An alternative to ITT analysis, the *per protocol* analytic procedure (i.e., analyses based
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37 on only "adherent" participants in randomized samples), has strengths as well and is of particular
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39 importance for hypotheses of an explanatory nature.¹² The per protocol approach can range from
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41 analyses in which only those research participants who began treatment are included, to those in
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43 which only participants who received what was deemed a "sufficient dose" of treatment are used,
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45 to those in which only participants who fully completed treatment are included (also referred to
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47 as a 'complete cases' approach).² Advocates of per protocol approach assert that the analysis
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49 tests the true efficacy of the intervention when used as directed (i.e., efficacy among those who
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51 are adherent and able to tolerate the treatment).
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3 Because both ITT and per protocol approaches to RCT analyses have their strengths, a
4 possible strategy is to conduct an ITT analysis, with a per protocol sensitivity analysis to
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6 “bracket” likely effects under different conditions. Nevertheless, ITT analyses are considered
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8 the "gold standard" and researchers frequently report the use of this procedure in published
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10 literature, even in the absence of a consensual definition. Discrepancies can arise, however,
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12 between the type of analyses researchers state in research reports that they conducted and what
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14 they *actually* did with respect to use of a “true” ITT analysis or some other procedure based on
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16 less than the full randomized sample. For example, in clinical trials in the nursing field, Polit
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18 and Gillespie⁸ found that for 10.5% of studies, researchers who stated they had used an ITT
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20 approach had actually conducted per protocol analyses.
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27 In this review, we examined discrepancies between the types of analyses that researchers
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29 stated they used and those they actually used in reports of a large pool of randomized controlled
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31 trials of pharmacotherapy for alcohol use disorders published between 1970 to 2009. We also
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33 examined the use of different missing data strategies in studies in which true and modified ITT
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35 analyses were and were not conducted. Finally, we examined whether the use of different data
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37 analytic approaches and certain types of missing data approaches (e.g., multiple imputation) has
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39 increased over time while the use of others has decreased.
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43 **Methods**

44 **Literature Search**

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46 As part of a larger project examining the efficacy of pharmacotherapies for alcohol use
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48 disorders and alcohol misuse,¹³ we identified relevant randomized controlled trials via several
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50 searches of PubMed and PsycINFO conducted at different points over the past decade. Study
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52 inclusion criteria were (a) a focus on treating alcohol misuse or an alcohol use disorder; (b)
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54 participants 18 years of age or older; (c) publication between 1970 and 2009; (d) a report in the
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3 English language; and (e) random assignment of at least five participants each to medication and
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6 placebo groups.

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

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

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47 (2) Full random sample (likely) - analyses appeared to use the full randomized sample,
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49 but N’s were not reported
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3 (3) Random sample followed-up - attempted to follow-up all randomized participants
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5 regardless of amount of medication/treatment completed and conducted analyses on this
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7 sample
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10 (4) Sufficient dose - analyses were conducted for only those participants who completed
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12 a specified amount of treatment or who received at least a minimum dose of treatment
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14 (5) Completer sample - analyses conducted for only those patients who completed the
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16 medication/treatment phase
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18 (6) False inclusion - after randomization, participants were found to not meet inclusion
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20 criteria and were subsequently removed from the analyses
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23 (7) Other - reported N's or degrees of freedom that were less than what would be
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25 expected for the randomized N, but no explanation of the participants included or
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27 excluded from the analysis was provided
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30 (8) Unclear – insufficient information was provided to determine the sample analyzed.
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34 Only analyses conducted on the Full Random Sample or Full Random Sample (likely) categories
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36 were deemed to be “true” ITT analyses, whereas the others were considered something other
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38 than ITT analyses.
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41 For those studies in which ITT analyses were actually conducted (i.e., “true” ITT with no
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43 missing outcome data due to 100% reassessment rate or imputing missing data), the categories
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45 for the “missing data strategy” variable were as follows:
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48 (1) No dropout – no dropout from treatment and 100% reassessed
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50 (2) All followed - there were drop-outs from treatment, but all participants, including
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52 treatment dropouts, were reassessed
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- 3 (3) Statistical imputation - used a statistical analysis that imputed missing data, e.g.,
- 4 mixed-model imputation
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- 8 (4) Failure assumed for missing data (missing = failure) - assumed that missing data
- 9 reflected poor outcome, e.g., relapse
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- 12 (5) Baseline assigned - a participant's baseline score was assigned if outcome data were
- 13 missing
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- 17 (6) LOCF - used the imputation strategy of Last Observation Carried Forward
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- 20 (7) Censored – last assessment point was used in survival analyses
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- 22 (8) Mean - used the mean of the sample followed for missing data
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- 24 (9) Other – used some other imputation of missing data strategy
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- 27 (10) Sample followed - conducted analyses with data for the sample of participants that
- 28 the researchers were able to follow/reassess
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- 31 (11) Unclear - no or unclear information provided.
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34 **Statistical Analyses**

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

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53 As noted in Table 1, a substantial discrepancy was evident between reporting an ITT
54 strategy versus actually conducting a “true” ITT analysis (i.e., reporting an ITT strategy when
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3 something other than ITT was conducted). Of the 165 studies included in this review, 74
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5 reported using an ITT strategy. However, less than half of those studies conducted a true ITT
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7 analysis ($K=29$; 39%) according to information in study reports. Interestingly, 35% ($K=32$) of the
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9 91 studies whose reports made *no* claim of using an ITT strategy, in fact, *did* perform true ITT
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11 analyses.
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Table 1.

Reported Using ITT	Conducted True ITT ^a	Sample Analyzed								Total Number of ITT and/or Non-ITT Approaches Used
		Full Random Sample	Full Random Sample (likely)	Random Sample FU	Sufficient Dose	Completer Sample	False Inclusion	Other	Unclear	
No (K=91)	32 (35%)	28 (25%)	4 (4%)	6 (5%)	19 (17%)	31 (28%)	2 (2%)	4 (4%)	16 (14%)	112
Yes (K=74)	29 (39%)	21 (21%)	9 (9%)	7 (7%)	40 (39%)	7 (7%)	8 (8%)	2 (2%)	0 (0%)	102
Total (K=165)	61 (37%)	49 (23%)	13 (6%)	13 (6%)	59 (28%)	38 (18%)	10 (5%)	6 (3%)	16 (8%)	214

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.

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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

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3 assuming missing equals relapse or some other poor outcome (“Failure”; $K=14$; 13%) and using
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5 a statistical imputation strategy ($K=14$; 13%), such as a mixed effects model. All other missing
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7 data strategies were utilized $\leq 10\%$ of the time, except the last observation carried forward
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9 (LOCF) procedure that was used in ($K=12$) 11% of the studies.
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Table 2.

Conducted True ITT	Missing Data Strategy											Total Number of ITT and/or Non-ITT Approaches Used
	No Tx or FU Dropout	All FU (some tx dropout)	Imputed	Missing = Failure	Baseline Assigned	LOCF	Censored (end of FU) Survival Analysis	Mean Substituted	Other	Sample FU	Unclear	
No (K=104)	0	0	6 (4%)	23 (17%)	1 (1%)	22 (16%)	25 (18%)	3 (2%)	2 (1%)	38 (27%)	17 (12%)	139
Yes (K=61)	1 (1%)	2 (2%)	14 (13%)	14 (13%)	1 (1%)	12 (11%)	23 (22%)	2 (2%)	1 (1%)	11 (10%)	24 (23%)	105
Total (K=165)	1 (>1%)	2 (>1%)	20 (07%)	37 (16%)	2 (>1%)	34 (13%)	48 (19%)	5 (2%)	3 (1%)	49 (19%)	41 (16%)	259 ^a

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.

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6 The most common missing data method utilized in studies not conducting a true ITT
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8 analysis was analyzing the sample followed-up ($K=38$; 27%), followed by censoring at the end
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10 of FU procedure ($K=25$; 18%), assuming failure (“Failure”; $K=23$; 17%), last observation carried
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12 forward ($K=23$; 16%) and an unclear strategy ($K=17$; 12%). All other missing data strategies
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14 were used $\leq 10\%$ of the time. A study could be categorized as *not* employing an ITT strategy, but
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16 still using a missing data strategy of assuming failure or last observation carried forward if, for
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18 example, the study assumed failure for missing participants, but something less than the full
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20 randomized N s were reported for analyses. Tables 3 and 4 display changes in ITT analyses and
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22 missing data strategies over time. No statistically significant changes were found in use of true
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24 ITT analyses over time (Table 3). However, several statistically significant relationships between
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26 missing data strategy and time emerged, as displayed in Table 4. Specifically, censored at end of
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28 FU (for survival analyses), last observation carried forward (LOCF), and using a statistical
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30 analysis to impute missing data (Imputed, e.g., mixed-model) have become more common over
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32 time, whereas analyses conducted on the sample of participants that the researchers were able to
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34 follow-up (Sample FU) has become less common.
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Table 3. Change in true ITT analyses over time

	Estimate	SE	t-value	P
(Intercept)	-1.44	0.62	-2.33	0.02*
Year	0.03	0.02	1.54	0.12

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

Table 4. Change in missing data strategy over time

	Estimate	SE	z-value	P
Fail	0.03	0.02	1.38	0.16
All FU	-0.10	0.09	-1.18	0.24
All FU (some dropout)	-0.09	0.06	-1.43	0.15
Baseline Assigned	0.47	0.36	1.31	0.19
Censored (end of FU)	0.09	0.03	3.19	<0.01**
LOCF	0.06	0.03	2.01	0.045*
Grp Avg	0.07	0.12	0.62	0.54
Mean FU points	0.07	0.07	0.92	0.36
Other	0.05	0.09	0.55	0.59
Sample FU	-0.10	0.02	-4.40	<0.001***
Imputed	0.33	0.09	3.83	<0.001***
Unclear	0.02	0.02	0.94	0.35

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.

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3 Because missing data strategies are becoming more sophisticated and are being facilitated
4 by computer technology that is easily able to process data using complex algorithms, the
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6 diversity of missing data strategies that are employed is increasing in number. Indeed, our
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8 findings indicate that more complex imputation procedures are becoming more prevalent over
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10 time. One such imputation procedure is Multiple Imputation³, which involves a Bayesian
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12 estimation procedure to average outcomes across multiple imputed datasets. Missing data are
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14 then replaced with a probable value based on other available variables in the data. Presumably,
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16 the results with this approach more closely approximate the results of an ITT analysis with 100%
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18 follow-up than any other method of handling missing data that is currently available.
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24 **Conclusion**

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27 Discrepancies in reporting versus actually conducting true ITT analyses were apparent in
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29 this body of alcohol pharmacotherapy trials. Lack of clarity regarding the missing data strategy
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31 used also was common. The degree to which these problems are present in reports of trials of
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33 pharmacotherapies and psychosocial interventions for other conditions remains to be determined.
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35 In addition, consensus on a standard definition of ITT is needed, as are clearer reporting
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37 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.

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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. 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.

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Clearer reporting standards for analyses and the handling of missing data in pharmacotherapy trials and other intervention studies are needed.

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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]

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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.

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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

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3 receipt of treatment/control condition) and (2) providing a more realistic estimate of average
4 treatment effects in the "real-world" as it is the norm for some patients to dropout or not adhere
5 to treatment. [1] Both points above address the issue of patient dropout, as analyses on only
6 adherent patients likely would lead to inflated estimates of treatment effects. Research has shown
7 that adherent patients generally do better than non-adherent patients, regardless of treatment.
8 [10,11] The more realistic estimates of treatment effects under conditions of routine care that are
9 derived from ITT analyses have particular relevance for policy makers and those interested in
10 hypotheses of pragmatic ("real world") importance.
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22 A variant of the ITT approach, what Polit and Gillespie (2010) term a "modified ITT"
23 analysis, maintains the conditions to which people were randomly assigned and attempts to
24 follow-up all participants, regardless of their participation in the intervention. However, only
25 those successfully followed are included in the analyses. With this modified approach, however,
26 the balance in pre-existing characteristics across conditions sought through random assignment is
27 less likely to hold.
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36 An alternative to ITT analysis, the *per protocol* analytic procedure (i.e., analyses based
37 on only "adherent" participants in randomized samples), has strengths as well and is of particular
38 importance for hypotheses of an explanatory nature.[12] The per protocol approach can range
39 from analyses in which only those research participants who began treatment are included, to
40 those in which only participants who received what was deemed a "sufficient dose" of treatment
41 are used, to those in which only participants who fully completed treatment are included also
42 referred to as a 'complete cases' approach[also referred to as a 'complete cases' approach; 2].
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53 Advocates of per protocol approach assert that the analysis tests the true efficacy of the
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3 intervention when used as directed (i.e., efficacy among those who are adherent and able to
4 tolerate the treatment).
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8 Because both ITT and per protocol approaches to RCT analyses have their strengths, a
9 possible strategy is to conduct an ITT analysis, with a per protocol sensitivity analysis to
10 “bracket” likely effects under different conditions. Nevertheless, ITT analyses are considered
11 the "gold standard" and researchers frequently report the use of this procedure in published
12 literature, even in the absence of a consensual definition. Discrepancies can arise, however,
13 between the type of analyses researchers state in research reports that they conducted and what
14 they *actually* did with respect to use of a “true” ITT analysis or some other procedure based on
15 less than the full randomized sample. For example, in clinical trials in the nursing field, Polit
16 and Gillespie (2009) found that for 10.5% of studies, researchers who stated they had used an
17 ITT approach had actually conducted per protocol analyses.
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32 It is unknown to what degree ITT strategies are being employed in pharmacotherapy for
33 alcohol use disorders. One aim of this review was to determine if there are discrepancies between
34 the types of analyses that researchers stated they used and those they actually used, based on
35 information in reports of a large pool of randomized controlled trials of pharmacotherapy for
36 alcohol use disorders published between 1970 to 2009. A second aim was to describe the use of
37 different missing data strategies in studies in which true and modified ITT analyses were and
38 were not conducted. The final aim was to determine whether the use of different data analytic
39 approaches and certain types of missing data approaches (e.g., multiple imputation) has
40 increased over time while the use of others has decreased.
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52 **Methods**

53 **Literature Search**

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

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50 Descriptive and inferential statistics were generated for two categorical variables: (1) sample
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52 analyzed and (2) missing data strategy. The categories of the “sample analyzed” variable were:
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3 (1) Full random sample - analyses involved the total randomized N's (with or without
4 imputation of missing data)
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8 (2) Full random sample (likely) - analyses appeared to use the full randomized sample,
9 but N's were not reported
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12 (3) Random sample followed-up - attempted to follow-up all randomized participants
13 regardless of amount of medication/treatment completed and conducted analyses on this
14 sample
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18 (4) Sufficient dose - analyses were conducted for only those participants who completed
19 a specified amount of treatment or who received at least a minimum dose of treatment
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23 (5) Completer sample - analyses conducted for only those patients who completed the
24 medication/treatment phase
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28 (6) False inclusion - after randomization, participants were found to not meet inclusion
29 criteria and were subsequently removed from the analyses
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33 (7) Other - reported N's or degrees of freedom that were less than what would be
34 expected for the randomized N, but no explanation of the participants included or
35 excluded from the analysis was provided
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39 (8) Unclear – insufficient information was provided to determine the sample analyzed.
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43 Only analyses conducted on the Full Random Sample or Full Random Sample (likely) categories
44 were deemed to be “true” ITT analyses, whereas the others were considered something other
45 than ITT analyses.
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50 The categories for the “missing data strategy” variable were as follows:
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53 (1) No dropout – no dropout from treatment and 100% reassessed
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- (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

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3 As noted in Table 1, a substantial discrepancy was evident between reporting an ITT
4 strategy versus actually conducting a “true” ITT analysis (i.e., reporting an ITT strategy when
5 something other than ITT was conducted). Of the 165 studies included in this review, 74
6 reported using an ITT strategy. However, less than half of those studies conducted a true ITT
7 analysis ($K=29$; 39%) according to information in study reports. Interestingly, 35% ($K=32$) of the
8 91 studies whose reports made *no* claim of using an ITT strategy, in fact, *did* perform true ITT
9 analyses.
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Table 1.

Reported Using ITT	Conducted True ITT ^a	Sample Analyzed								Total Number of ITT and/or Non-ITT Approaches Used
		Full Random Sample	Full Random Sample (likely)	Random Sample FU	Sufficient Dose	Completer Sample	False Inclusion	Other	Unclear	
No (K=91)	32 (35%)	28 (25%)	4 (4%)	6 (5%)	19 (17%)	31 (28%)	2 (2%)	4 (4%)	16 (14%)	112
Yes (K=74)	29 (39%)	21 (21%)	9 (9%)	7 (7%)	40 (39%)	7 (7%)	8 (8%)	2 (2%)	0 (0%)	102
Total (K=165)	61 (37%)	49 (23%)	13 (6%)	13 (6%)	59 (28%)	38 (18%)	10 (5%)	6 (3%)	16 (8%)	214

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.

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6 Regarding the specific data analytic strategy used, the values in each row of Table 1 do
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8 not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45
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10 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming
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12 failure for dichotomous outcomes AND also used a complete cases approach for continuous
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14 outcomes). In such instances, we coded "Reported Using ITT" as "Yes" if the study mentioned
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16 using an ITT strategy and coded it as "No" otherwise (i.e., no mention of using an ITT strategy).
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20 The most common approach utilized in studies reporting the use of an ITT strategy, other
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22 than use of a true ITT ($K=29$; 39%), involved analyses of data for participants who completed a
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24 "sufficient dose" of the medication/treatment ($K=40$; 39%). All other strategies were utilized
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26 <10% of the time. The most common analytic method used in studies not mentioning an ITT
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28 strategy was actually a true ITT analysis ($K=32$; 29%), followed by analyses of data from
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30 completer samples ($K=31$; 28%), analyses for participants who completed a "sufficient dose" of
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32 medication/treatment ($K=19$; 17%), and indeterminable strategies (i.e., Unclear; $K=16$; 14%).
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36 Table 2 reports the descriptive information on the missing data strategies employed in the
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38 studies using and not using a true ITT approach. Similar to Table 1, the values in each row of
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40 Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due
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42 to 42 studies utilizing multiple missing data strategies. The most common missing data strategy
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44 utilized in studies employing an ITT approach was either unclear ($K=24$; 23%) or involved
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46 censoring data at the end of FU procedure in survival analyses ($K=23$; 22%). A study could be
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48 categorized as employing an ITT strategy, but having an unclear missing data strategy if, for
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50 example, the study reported the full randomized N s from analyses, but it was unclear what
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52 particular missing data strategy was utilized. The next most frequently used strategies were
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3 assuming missing equals relapse or some other poor outcome (“Failure”; $K=14$; 13%) and using
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5 a statistical imputation or interpolation strategy ($K=14$; 13%), such as a mixed effects model. All
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8 other missing data strategies were utilized $\leq 10\%$ of the time, except the last observation carried
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10 forward (LOCF) procedure that was used in ($K=12$) 11% of the studies.
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Table 2.

Conducted True ITT	Missing Data Strategy											Total Number of ITT and/or Non-ITT Approaches Used
	No Tx or FU Dropout	All FU (some tx dropout)	Imputation or Interpolation	Missing = Failure	Baseline Assigned	LOCF	Censored (end of FU) Survival Analysis	Mean Substituted	Other	Sample FU	Unclear	
No (K=104)	0	0	6 (4%)	23 (17%)	1 (1%)	22 (16%)	25 (18%)	3 (2%)	2 (1%)	38 (27%)	17 (12%)	139
Yes (K=61)	1 (1%)	2 (2%)	14 (13%)	14 (13%)	1 (1%)	12 (11%)	23 (22%)	2 (2%)	1 (1%)	11 (10%)	24 (23%)	105
Total (K=165)	1 (>1%)	2 (>1%)	20 (07%)	37 (16%)	2 (>1%)	34 (13%)	48 (19%)	5 (2%)	3 (1%)	49 (19%)	41 (16%)	259 ^a

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).

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6 The most common missing data method utilized in studies not conducting a true ITT
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8 analysis was analyzing the sample followed-up ($K=38$; 27%), followed by censoring at the end
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10 of FU procedure ($K=25$; 18%), assuming failure (“Failure”; $K=23$; 17%), last observation carried
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12 forward ($K=23$; 16%) and an unclear strategy ($K=17$; 12%). All other missing data strategies
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14 were used $\leq 10\%$ of the time. A study could be categorized as *not* employing an ITT strategy, but
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16 still using a missing data strategy of assuming failure or last observation carried forward if, for
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18 example, the study assumed failure for missing participants, but something less than the full
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20 randomized N s were reported for analyses. Tables 3 and 4 display changes in ITT analyses and
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22 missing data strategies over time. No statistically significant change (although marginally
23
24 significant trend) was found in use of true ITT analyses over time (Table 3). This relationship is
25
26 depicted graphically with time on the x -axis, probability (of being an ITT) from generalized
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28 linear model results on the y -axis, and raw study values (0= not ITT, 1=ITT) displayed as points.
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30 The 95% confidence intervals are displayed as a grey line around the probability slope.
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37 Several statistically significant relationships between missing data strategy and time
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39 emerged, as displayed in Table 4. Specifically, censored at end of FU (for survival analyses), last
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41 observation carried forward (LOCF), and using a statistical analysis to impute/interpolate
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43 missing data (Imputed/Interpolated, e.g., mixed-model interpolation) have become more
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45 common over time, whereas analyses conducted on only the samples of participants that the
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47 researchers were able to follow-up (Sample FU) has become less common. To explore whether
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49 increasing use of certain missing data strategies over time was confounded with longitudinal
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51 methods being increasingly employed, a proxy dummy control variable (0=only end-of treatment
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3 assessment, 1= posttreatment and follow-up assessment(s)) was added to the analyses; the results
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5 were virtually unchanged.
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Table 3. Change in true ITT analyses over time

	Estimate	SE	t-value	P
(Intercept)	-1.52	0.64	-2.39	0.02*
Year	0.04	0.02	1.85	0.06

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

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

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.

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3 Because missing data strategies are becoming more sophisticated and are being facilitated
4 by computer technology that is easily able to process data using complex algorithms, the
5 diversity of missing data strategies that are employed is increasing. Indeed, our findings indicate
6 that more complex imputation procedures are becoming more prevalent over time. One such
7 imputation procedure is Multiple Imputation, [3] which involves a Bayesian estimation
8 procedure to average outcomes across multiple imputed datasets. Missing data are then replaced
9 with a probable value based on other available variables in the data. Presumably, the results with
10 this approach more closely approximate the results of an ITT analysis with 100% follow-up than
11 any other method of handling missing data that is currently available.
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24 **Conclusion**

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27 Discrepancies in reporting versus actually conducting true ITT analyses were apparent in
28 this body of alcohol pharmacotherapy trials. Lack of clarity regarding the missing data strategy
29 used also was common. The degree to which these problems are present in reports of trials of
30 pharmacotherapies and psychosocial interventions for other conditions remains to be determined.
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32 In addition, consensus on a standard definition of ITT is needed, as are clearer reporting
33 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.

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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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Abstract

Objectives~~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 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~~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.

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~~.

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9 | Conclusions~~Conclusion~~: Discrepancies in reporting versus actually conducting ITT analyses
10 were found in this body of RCTs. Lack of clarity regarding the missing data strategy used was
11 common. Consensus on a definition of ITT is important for adequate understanding of research
12 findings. Clearer reporting standards for analyses and the handling of missing data in
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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 ~~inbetween~~ 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] (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

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9 receipt of treatment/control condition) and (2) providing a more realistic estimate of average
10 treatment effects in the "real-world" as it is the norm for some patients to dropout or not adhere
11 to treatment. ^[1] Both points above address the issue of patient dropout, as analyses on only
12 adherent patients likely would lead to inflated estimates of treatment effects. Research has shown
13 that adherent patients generally do better than non-adherent patients, regardless of treatment.
14 ~~[10,11](Avins et al., 2010; Granger et al., 2006).~~ The more realistic estimates of treatment effects
15 under conditions of routine care that are derived from ITT analyses have particular relevance for
16 policy makers and those interested in hypotheses of pragmatic ("real world") importance.
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24 A variant of the ITT approach, what Polit and Gillespie (2010) term a "modified ITT"
25 analysis, maintains the conditions to which people were randomly assigned and attempts to
26 follow-up all participants, regardless of their participation in the intervention. However, only
27 those successfully followed are included in the analyses. With this modified approach, however,
28 the balance in pre-existing characteristics across conditions sought through random assignment is
29 less likely to hold.
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35 An alternative to ITT analysis, the *per protocol* analytic procedure (i.e., analyses based
36 on only "adherent" participants in randomized samples), has strengths as well and is of particular
37 importance for hypotheses of an explanatory nature. ~~[12](Schwartz and Lellouch, 1967).~~ The per
38 protocol approach can range from analyses in which only those research participants who began
39 treatment are included, to those in which only participants who received what was deemed a
40 "sufficient dose" of treatment are used, to those in which only participants who fully completed
41 treatment are included also referred to as a 'complete cases' approach. ~~[also referred to as a~~
42 'complete cases' approach; ^{2]}. Advocates of per protocol approach assert that the analysis tests
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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

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

45 **Variables**

46 Descriptive and inferential statistics were generated for two categorical variables: (1) sample
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48 analyzed and (2) missing data strategy. -The categories of the “sample analyzed” variable were:
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- 9 (1) Full random sample - analyses involved the total randomized N's (with or without
- 10 imputation of missing data)
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- 12 (2) Full random sample (likely) - analyses appeared to use the full randomized sample,
- 13 but N's were not reported
- 14
- 15 (3) Random sample followed-up - attempted to follow-up all randomized participants
- 16 regardless of amount of medication/treatment completed and conducted analyses on this
- 17 sample
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- 19 (4) Sufficient dose - analyses were conducted for only those participants who completed
- 20 a specified amount of treatment or who received at least a minimum dose of treatment
- 21
- 22 (5) Completer sample - analyses conducted for only those patients who completed the
- 23 medication/treatment phase
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- 25 (6) False inclusion - after randomization, participants were found to not meet inclusion
- 26 criteria and were subsequently removed from the analyses
- 27
- 28 (7) Other - reported N's or degrees of freedom that were less than what would be
- 29 expected for the randomized N, but no explanation of the participants included or
- 30 excluded from the analysis was provided
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- 32 (8) Unclear – insufficient information was provided to determine the sample analyzed.
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41 Only analyses conducted on the Full Random Sample or Full Random Sample (likely) categories
42 were deemed to be “true” ITT analyses, whereas the others were considered something other
43 than ITT analyses.
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46 ~~The~~For those studies in which ITT analyses were actually conducted (i.e., “true” ITT
47 ~~with no missing outcome data due to 100% reassessment rate or imputing missing data), the~~
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49 categories for the “missing data strategy” variable were as follows:
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- (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.

Reported Using ITT	Conducted True ITT ^a	Sample Analyzed								Total Number of ITT and/or Non-ITT Approaches Used
		Full Random Sample	Full Random Sample (likely)	Random Sample FU	Sufficient Dose	Completer Sample	False Inclusion	Other	Unclear	
No	32	28	4	6	19	31	2	4	16	112
(K=91)	(35%)	(25%)	(4%)	(5%)	(17%)	(28%)	(2%)	(4%)	(14%)	
Yes	29	21	9	7	40	7	8	2	0	102
(K=74)	(39%)	(21%)	(9%)	(7%)	(39%)	(7%)	(8%)	(2%)	(0%)	
Total	61	49	13	13	59	38	10	6	16	214
(K=165)	(37%)	(23%)	(6%)	(6%)	(28%)	(18%)	(5%)	(3%)	(8%)	

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.

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11 Regarding the specific data analytic strategy used, the values in each row of Table 1 do
12 not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45
13 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming
14 failure for dichotomous outcomes AND also used a complete cases approach for continuous
15 outcomes). In such instances, we coded "Reported Using ITT" as "Yes" if the study mentioned
16 using an ITT strategy and coded it as "No" otherwise (i.e., no mention of using an ITT strategy).
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22 The most common approach utilized in studies reporting the use of an ITT strategy, other
23 than use of a true ITT ($K=29$; 39%), involved analyses of data for participants who completed a
24 "sufficient dose" of the medication/treatment ($K=40$; 39%). All other strategies were utilized
25 <10% of the time. The most common analytic method used in studies not mentioning an ITT
26 strategy was actually a true ITT analysis ($K=32$; 29%), followed by analyses of data from
27 completer samples ($K=31$; 28%), analyses for participants who completed a "sufficient dose" of
28 medication/treatment ($K=19$; 17%), and indeterminable strategies (i.e., Unclear; $K=16$; 14%).
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35 Table 2 reports the descriptive information on the missing data strategies employed in the
36 studies using and not using a true ITT approach. Similar to Table 1, the values in each row of
37 Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due
38 to 42 studies utilizing multiple missing data strategies. The most common missing data strategy
39 utilized in studies employing an ITT approach was either unclear ($K=24$; 23%) or involved
40 censoring data at the end of FU procedure in survival analyses ($K=23$; 22%). A study could be
41 categorized as employing an ITT strategy, but having an unclear missing data strategy if, for
42 example, the study reported the full randomized N s from analyses, but it was unclear what
43 particular missing data strategy was utilized. The next most frequently used strategies were
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9 assuming missing equals relapse or some other poor outcome (“Failure”; $K=14$; 13%) and using
10 a statistical imputation or interpolation strategy ($K=14$; 13%), such as a mixed effects model. All
11 other missing data strategies were utilized $\leq 10\%$ of the time, except the last observation carried
12 forward (LOCF) procedure that was used in ($K=12$) 11% of the studies.
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Table 2.

Conducted True ITT	Missing Data Strategy											Total Number of ITT and/or Non-ITT Approaches Used
	No Tx or FU Dropout	All FU (some tx dropout)	Imputation or Interpolation Imputed	Missing = Failure	Baseline Assigned	LOCF	Censored (end of FU) Survival Analysis	Mean Substituted	Other	Sample FU	Unclear	
No (K=104)	0	0	6 (4%)	23 (17%)	1 (1%)	22 (16%)	25 (18%)	3 (2%)	2 (1%)	38 (27%)	17 (12%)	139
Yes (K=61)	1 (1%)	2 (2%)	14 (13%)	14 (13%)	1 (1%)	12 (11%)	23 (22%)	2 (2%)	1 (1%)	11 (10%)	24 (23%)	105
Total (K=165)	1 (>1%)	2 (>1%)	20 (07%)	37 (16%)	2 (>1%)	34 (13%)	48 (19%)	5 (2%)	3 (1%)	49 (19%)	41 (16%)	259 ^a

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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.~~

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11 The most common missing data method utilized in studies not conducting a true ITT
12 analysis was analyzing the sample followed-up ($K=38$; 27%), followed by censoring at the end
13 of FU procedure ($K=25$; 18%), assuming failure (“Failure”; $K=23$; 17%), last observation carried
14 forward ($K=23$; 16%) and an unclear strategy ($K=17$; 12%). All other missing data strategies
15 were used $\leq 10\%$ of the time. A study could be categorized as *not* employing an ITT strategy, but
16 still using a missing data strategy of assuming failure or last observation carried forward if, for
17 example, the study assumed failure for missing participants, but something less than the full
18 randomized N s were reported for analyses. Tables 3 and 4 display changes in ITT analyses and
19 missing data strategies over time. No statistically significant change (although marginally
20 significant trend) was changes were found in use of true ITT analyses over time (Table 3). This
21 relationship is depicted graphically with time on the x-axis, probability (of being an ITT) from
22 generalized linear model results on the y-axis, and raw study values (0= not ITT, 1=ITT)
23 displayed as points. The 95% confidence intervals are displayed as a grey line around the
24 probability slope.

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

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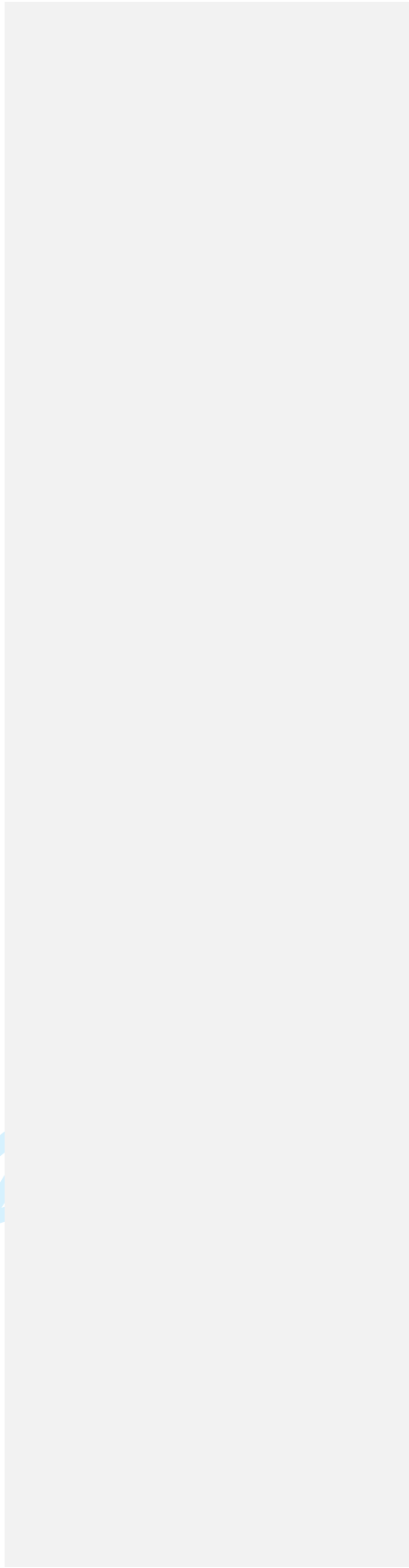


Table 3. Change in true ITT analyses over time

	Estimate	SE	t-value	P
(Intercept)	-1.5244	0.6462	-2.3933	0.02*
Year	0.0403	0.02	1.8554	0.0642

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

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

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

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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.

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9 Because missing data strategies are becoming more sophisticated and are being facilitated
10 by computer technology that is easily able to process data using complex algorithms, the
11 diversity of missing data strategies that are employed is increasing ~~in number~~. Indeed, our
12 findings indicate that more complex imputation procedures are becoming more prevalent over
13 time. One such imputation procedure is Multiple Imputation, [3] which involves a Bayesian
14 estimation procedure to average outcomes across multiple imputed datasets. Missing data are
15 then replaced with a probable value based on other available variables in the data. Presumably,
16 the results with this approach more closely approximate the results of an ITT analysis with 100%
17 follow-up than any other method of handling missing data that is currently available.
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25 **Conclusion**

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

10 No ethics approval was required for completion of this study. It aggregated previously published
11 journal articles.
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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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33 Keywords: intention to treat, missing data strategies, research methods
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36 Word count: 3,557, abstract: 298, references: 12, tables: 4
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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 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.

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3 Clearer reporting standards for analyses and the handling of missing data in pharmacotherapy
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5 trials and other intervention studies are needed.
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10 **Strengths and Limitations**

13 Strengths

- 14 • First study to examine ITT practices in RCT pharmacotherapy trials for alcohol misuse.
- 15 • Included a large body of studies in the analyses.
- 16 • Examined changes over time in data analytic and missing data strategies across nearly 40
- 17 years of scientific research.
- 18 • Findings important for improving reporting practices in RCTs of pharmacotherapy trials
- 19 for alcohol misuse.
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25 Limitations

- 26 • Descriptive analyses could not determine whether there is any relationship between ITT
- 27 and effect sizes.
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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]

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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.

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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

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3 receipt of treatment/control condition) and (2) providing a more realistic estimate of average
4 treatment effects in the "real-world" as it is the norm for some patients to dropout or not adhere
5 to treatment. [1] Both points above address the issue of patient dropout, as analyses on only
6 adherent patients likely would lead to inflated estimates of treatment effects. Research has shown
7 that adherent patients generally do better than non-adherent patients, regardless of treatment.
8 [10,11] The more realistic estimates of treatment effects under conditions of routine care that are
9 derived from ITT analyses have particular relevance for policy makers and those interested in
10 hypotheses of pragmatic ("real world") importance.
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22 A variant of the ITT approach, what Polit and Gillespie (2010) term a "modified ITT"
23 analysis, maintains the conditions to which people were randomly assigned and attempts to
24 follow-up all participants, regardless of their participation in the intervention. However, only
25 those successfully followed are included in the analyses. With this modified approach, however,
26 the balance in pre-existing characteristics across conditions sought through random assignment is
27 less likely to hold.
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36 An alternative to ITT analysis, the *per protocol* analytic procedure (i.e., analyses based
37 on only "adherent" participants in randomized samples), has strengths as well and is of particular
38 importance for hypotheses of an explanatory nature.[12] The per protocol approach can range
39 from analyses in which only those research participants who began treatment are included, to
40 those in which only participants who received what was deemed a "sufficient dose" of treatment
41 are used, to those in which only participants who fully completed treatment are included [also
42 referred to as a 'complete cases' approach; 2]. Advocates of per protocol approach assert that the
43 analysis tests the true efficacy of the intervention when used as directed (i.e., efficacy among
44 those who are adherent and able to tolerate the treatment).
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3 Because both ITT and per protocol approaches to RCT analyses have their strengths, a
4 possible strategy is to conduct an ITT analysis, with a per protocol sensitivity analysis to
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6 “bracket” likely effects under different conditions. Nevertheless, ITT analyses are considered
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8 the "gold standard" and researchers frequently report the use of this procedure in published
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10 literature, even in the absence of a consensual definition. Discrepancies can arise, however,
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12 between the type of analyses researchers state in research reports that they conducted and what
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14 they *actually* did with respect to use of a “true” ITT analysis or some other procedure based on
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16 less than the full randomized sample. For example, in clinical trials in the nursing field, Polit
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18 and Gillespie (2009) found that for 10.5% of studies, researchers who stated they had used an
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20 ITT approach had actually conducted per protocol analyses.
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27 It is unknown to what degree ITT strategies are being employed in pharmacotherapy for
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29 alcohol use disorders. One aim of this review was to determine if there are discrepancies between
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31 the types of analyses that researchers stated they used and those they actually used, based on
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33 information in reports of a large pool of randomized controlled trials of pharmacotherapy for
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35 alcohol use disorders published between 1970 to 2009. A second aim was to describe the use of
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37 different missing data strategies in studies in which true and modified ITT analyses were and
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39 were not conducted. The final aim was to determine whether the use of different data analytic
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41 approaches and certain types of missing data approaches (e.g., multiple imputation) has
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43 increased over time while the use of others has decreased.
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48 **Methods**

49 **Literature Search**

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

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

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49 (1) Full random sample - analyses involved the total randomized N’s (with or without
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51 imputation or interpolation of missing data).
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3 (2) Full random sample (likely) - analyses appeared to use the full randomized sample,
4 but N's were not reported.
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8 (3) Random sample followed-up - attempted to follow-up all randomized participants.
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10 regardless of amount of medication/treatment completed and conducted analyses on this
11 sample. Note there is no overlap between categories 1 ("Full random sample") or 2 ("Full
12 random sample (likely)") and "Random sample followed-up".
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16 (4) Sufficient dose - analyses were conducted for only those participants who completed
17 a specified amount of treatment or who received at least a minimum dose of treatment.
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21 (5) Completer sample - analyses conducted for only those patients who completed the
22 medication/treatment phase.
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26 (6) False inclusion - after randomization, participants were found to not meet inclusion
27 criteria and were subsequently removed from the analyses.
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31 (7) Other - reported N's or degrees of freedom that were less than what would be
32 expected for the randomized N, but no explanation of the participants included or
33 excluded from the analysis was provided.
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38 (8) Unclear – insufficient information was provided to determine the sample analyzed.
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41 Only analyses conducted on the Full Random Sample or Full Random Sample (likely) categories
42 were deemed to be “true” ITT analyses, whereas the others were considered something other
43 than ITT analyses.
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48 The categories for the “missing data strategy” variable were as follows:
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50 (1) No dropout – no dropout from treatment and 100% reassessed.
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52 (2) All followed - there were drop-outs from treatment, but all participants, including
53 treatment dropouts, were reassessed.
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- (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

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3 something other than ITT was conducted). Of the 165 studies included in this review, 74
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5 reported using an ITT strategy. However, less than half of those studies conducted a true ITT
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7 analysis ($K=29$; 39%) according to information in study reports. Interestingly, 35% ($K=32$) of the
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9 91 studies whose reports made *no* claim of using an ITT strategy, in fact, *did* perform true ITT
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11 analyses.
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Table 1.

Reported Using ITT	Conducted True ITT ^a	Sample Analyzed								Total Number of ITT and/or Non-ITT Approaches Used
		Full Random Sample	Full Random Sample (likely)	Random Sample FU	Sufficient Dose	Completer Sample	False Inclusion	Other	Unclear	
No (K=91)	32 (35%)	28 (25%)	4 (4%)	6 (5%)	19 (17%)	31 (28%)	2 (2%)	4 (4%)	16 (14%)	112
Yes (K=74)	29 (39%)	21 (21%)	9 (9%)	7 (7%)	40 (39%)	7 (7%)	8 (8%)	2 (2%)	0 (0%)	102
Total (K=165)	61 (37%)	49 (23%)	13 (6%)	13 (6%)	59 (28%)	38 (18%)	10 (5%)	6 (3%)	16 (8%)	214

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.

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6 Regarding the specific data analytic strategy used, the values in each row of Table 1 do
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8 not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45
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10 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming
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12 failure for dichotomous outcomes AND also used a complete cases approach for continuous
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14 outcomes). In such instances, we coded "Reported Using ITT" as "Yes" if the study mentioned
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16 using an ITT strategy and coded it as "No" otherwise (i.e., no mention of using an ITT strategy).
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20 The most common approach utilized in studies reporting the use of an ITT strategy, other
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22 than use of a true ITT ($K=29$; 39%), involved analyses of data for participants who completed a
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24 "sufficient dose" of the medication/treatment ($K=40$; 39%). All other strategies were utilized
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26 <10% of the time. The most common analytic method used in studies not mentioning an ITT
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28 strategy was actually a true ITT analysis ($K=32$; 29%), followed by analyses of data from
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30 completer samples ($K=31$; 28%), analyses for participants who completed a "sufficient dose" of
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32 medication/treatment ($K=19$; 17%), and indeterminable strategies (i.e., Unclear; $K=16$; 14%).
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36 Table 2 reports the descriptive information on the missing data strategies employed in the
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38 studies using and not using a true ITT approach. Similar to Table 1, the values in each row of
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40 Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due
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42 to 42 studies utilizing multiple missing data strategies. The most common missing data strategy
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44 utilized in studies employing an ITT approach was either unclear ($K=24$; 23%) or involved
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46 censoring data at the end of FU procedure in survival analyses ($K=23$; 22%). A study could be
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48 categorized as employing an ITT strategy, but having an unclear missing data strategy if, for
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50 example, the study reported the full randomized N s from analyses, but it was unclear what
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52 particular missing data strategy was utilized. The next most frequently used strategies were
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3 assuming missing equals relapse or some other poor outcome (“Failure”; $K=14$; 13%) and using
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5 a statistical interpolation strategy ($K=14$; 13%), such as a mixed effects model. All other missing
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7 data strategies were utilized $\leq 10\%$ of the time, except the last observation carried forward
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9 (LOCF) procedure that was used in ($K=12$) 11% of the studies.
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Table 2.

Conducted True ITT	Missing Data Strategy											Total Number of ITT and/or Non-ITT Approaches Used
	No Tx or FU Dropout	All FU (some tx dropout)	Interpolation	Missing = Failure	Baseline Assigned	LOCF	Censored (end of FU) Survival Analysis	Mean Substituted	Other	Sample FU	Unclear	
No (K=104)	0	0	6 (4%)	23 (17%)	1 (1%)	22 (16%)	25 (18%)	3 (2%)	2 (1%)	38 (27%)	17 (12%)	139
Yes (K=61)	1 (1%)	2 (2%)	14 (13%)	14 (13%)	1 (1%)	12 (11%)	23 (22%)	2 (2%)	1 (1%)	11 (10%)	24 (23%)	105
Total (K=165)	1 (>1%)	2 (>1%)	20 (07%)	37 (16%)	2 (>1%)	34 (13%)	48 (19%)	5 (2%)	3 (1%)	49 (19%)	41 (16%)	259 ^a

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).

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6 The most common missing data method utilized in studies not conducting a true ITT
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8 analysis was analyzing the sample followed-up ($K=38$; 27%), followed by censoring at the end
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10 of FU procedure ($K=25$; 18%), assuming failure (“Failure”; $K=23$; 17%), last observation carried
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12 forward ($K=23$; 16%) and an unclear strategy ($K=17$; 12%). All other missing data strategies
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14 were used $\leq 10\%$ of the time. A study could be categorized as *not* employing an ITT strategy, but
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16 still using a missing data strategy of assuming failure or last observation carried forward if, for
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18 example, the study assumed failure for missing participants, but something less than the full
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20 randomized N s were reported for analyses. Tables 3 and 4 display changes in ITT analyses and
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22 missing data strategies over time. No statistically significant change (although marginally
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24 significant trend) was found in use of true ITT analyses over time (Table 3). This relationship is
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26 depicted graphically with time on the x -axis, probability (of being an ITT) from generalized
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28 linear model results on the y -axis, and raw study values (0= not ITT, 1=ITT) displayed as points.
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30 The 95% confidence intervals are displayed as a grey line around the probability slope.
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37 Several statistically significant relationships between missing data strategy and time
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39 emerged, as displayed in Table 4. Specifically, censored at end of FU (for survival analyses), last
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41 observation carried forward (LOCF), and using a statistical analysis to interpolate missing data
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43 (Interpolation, e.g., mixed effects model interpolation) have become more common over time,
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45 whereas analyses conducted on only the samples of participants that the researchers were able to
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47 follow-up (Sample FU) has become less common. To explore whether increasing use of certain
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49 missing data strategies over time was confounded with longitudinal methods being increasingly
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51 employed, a proxy dummy control variable (0=only end-of treatment assessment, 1=
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3 posttreatment and follow-up assessment(s)) was added to the analyses; the results were virtually
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5 unchanged.
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Table 3. Change in true ITT analyses over time

	Estimate	SE	t-value	P
(Intercept)	-1.52	0.64	-2.39	0.02*
Year	0.04	0.02	1.85	0.06

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

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

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.

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3 Because missing data strategies are becoming more sophisticated and are being facilitated
4 by computer technology that is easily able to process data using complex algorithms, the
5 diversity of missing data strategies that are employed is increasing. Indeed, our findings indicate
6 that more complex imputation or interpolation procedures are becoming more prevalent over
7 time. One such imputation procedure is Multiple Imputation, [3] which involves a Bayesian
8 estimation procedure to average outcomes across multiple imputed datasets. Missing data are
9 then replaced with a probable value based on other available variables in the data. Presumably,
10 the results with this approach more closely approximate the results of an ITT analysis with 100%
11 follow-up than any other method of handling missing data that is currently available.
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24 **Conclusion**

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27 Discrepancies in reporting versus actually conducting true ITT analyses were apparent in
28 this body of alcohol pharmacotherapy trials. Lack of clarity regarding the missing data strategy
29 used also was common. The degree to which these problems are present in reports of trials of
30 pharmacotherapies and psychosocial interventions for other conditions remains to be determined.
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32 In addition, consensus on a standard definition of ITT is needed, as are clearer reporting
33 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.

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12 A. C. Del Re was involved in the study's design, analysis and interpretation of data,
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14 drafting the article and revising it. Natalya C. Maisel was involved in the study's design and
15
16 revising the article. Janet Blodgett was involved in the study's design. John W. Finney was
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18 involved in the study's conception and design, interpretation of data, and revising it critically for
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9 Intention-to-Treat Analyses and Missing Data Approaches in Pharmacotherapy Trials for
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11 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~~ a strategy 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.

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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.

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9 In pharmacotherapy trials, participants typically are randomly assigned to a
10 pharmacotherapy or a placebo (control) condition. With a sufficient sample size, randomization
11 usually produces separate groups *without* systematic differences by equalizing factors within
12 groups that may be associated with outcome (e.g., motivation, age, gender). Under ideal
13 circumstances, the randomization process allows valid causal inferences to be made about the
14 impact of the pharmacotherapy compared to the control condition. That is, one can be highly
15 confident that any post-treatment differences in outcome are attributable to the impact of the
16 medication itself and not to pre-existing differences in the characteristics of the pharmacotherapy
17 and placebo samples. However, when the randomization process is disrupted, either through
18 treatment dropout and/or missing data on outcomes, or when the original sample as randomized
19 is not the same sample analyzed (analyzed N < randomized N), bias may be introduced that
20 compromises the internal validity of results. [1–4]
21

22 The intention-to-treat (ITT) analytic strategy is one solution for eliminating or reducing
23 bias in treatment effects arising from missing outcome data in randomized controlled trials
24 (RCTs). [1,2] Although no universally accepted definition of ITT currently exists, the procedure
25 nevertheless is endorsed in the Consolidated Standards for Reporting Trials (CONSORT). [5–7]
26 One particularly succinct definition of a "true ITT" [8] analysis is "once randomized, always
27 analyzed." [9] Under this definition, ITT involves analysis of *all* trial participants who were
28 randomized, regardless of adherence to treatment protocol (e.g., dropout/withdrawal or protocol
29 deviations). In other words, defined this way, ITT requires either no attrition or ~~some imputation~~
30 ~~procedure~~ strategy to ~~account for any~~ handle missing data.
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32 ITT has several strengths, including (1) helping to preserve the integrity of the
33 randomization process (i.e., groups are expected to be similar except for random variation and
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9 receipt of treatment/control condition) and (2) providing a more realistic estimate of average
10 treatment effects in the "real-world" as it is the norm for some patients to dropout or not adhere
11 to treatment. [1] Both points above address the issue of patient dropout, as analyses on only
12 adherent patients likely would lead to inflated estimates of treatment effects. Research has shown
13 that adherent patients generally do better than non-adherent patients, regardless of treatment.
14 [10,11] The more realistic estimates of treatment effects under conditions of routine care that are
15 derived from ITT analyses have particular relevance for policy makers and those interested in
16 hypotheses of pragmatic ("real world") importance.
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24 A variant of the ITT approach, what Polit and Gillespie (2010) term a "modified ITT"
25 analysis, maintains the conditions to which people were randomly assigned and attempts to
26 follow-up all participants, regardless of their participation in the intervention. However, only
27 those successfully followed are included in the analyses. With this modified approach, however,
28 the balance in pre-existing characteristics across conditions sought through random assignment is
29 less likely to hold.
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36 An alternative to ITT analysis, the *per protocol* analytic procedure (i.e., analyses based
37 on only "adherent" participants in randomized samples), has strengths as well and is of particular
38 importance for hypotheses of an explanatory nature.[12] The per protocol approach can range
39 from analyses in which only those research participants who began treatment are included, to
40 those in which only participants who received what was deemed a "sufficient dose" of treatment
41 are used, to those in which only participants who fully completed treatment are included ~~also~~
42 referred to as a 'complete cases' approach [also referred to as a 'complete cases' approach; 2].
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9 intervention when used as directed (i.e., efficacy among those who are adherent and able to
10 tolerate the treatment).
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12 Because both ITT and per protocol approaches to RCT analyses have their strengths, a
13 possible strategy is to conduct an ITT analysis, with a per protocol sensitivity analysis to
14 “bracket” likely effects under different conditions. Nevertheless, ITT analyses are considered
15 the “gold standard” and researchers frequently report the use of this procedure in published
16 literature, even in the absence of a consensual definition. Discrepancies can arise, however,
17 between the type of analyses researchers state in research reports that they conducted and what
18 they *actually* did with respect to use of a “true” ITT analysis or some other procedure based on
19 less than the full randomized sample. For example, in clinical trials in the nursing field, Polit
20 and Gillespie (2009) found that for 10.5% of studies, researchers who stated they had used an
21 ITT approach had actually conducted per protocol analyses.
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31 It is unknown to what degree ITT strategies are being employed in pharmacotherapy for
32 alcohol use disorders. One aim of this review was to determine if there are discrepancies between
33 the types of analyses that researchers stated they used and those they actually used, based on
34 information in reports of a large pool of randomized controlled trials of pharmacotherapy for
35 alcohol use disorders published between 1970 to 2009. A second aim was to describe the use of
36 different missing data strategies in studies in which true and modified ITT analyses were and
37 were not conducted. The final aim was to determine whether the use of different data analytic
38 approaches and certain types of missing data approaches (e.g., multiple imputation) has
39 increased over time while the use of others has decreased.
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48 **Methods**

49 **Literature Search**

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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~~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:

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9 (1) Full random sample - analyses involved the total randomized N's (with or without
10 imputation or interpolation of missing data).
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13 (2) Full random sample (likely) - analyses appeared to use the full randomized sample,
14 but N's were not reported.
- 15
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17 (3) Random sample followed-up - attempted to follow-up all randomized participants,
18 regardless of amount of medication/treatment completed and conducted analyses on this
19 sample. Note there is no overlap between categories 1 ("Full random sample") or 2 ("Full
20 random sample (likely)") and "Random sample followed-up".
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23 (4) Sufficient dose - analyses were conducted for only those participants who completed
24 a specified amount of treatment or who received at least a minimum dose of treatment.
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27 (5) Completer sample - analyses conducted for only those patients who completed the
28 medication/treatment phase.
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31 (6) False inclusion - after randomization, participants were found to not meet inclusion
32 criteria and were subsequently removed from the analyses.
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35 (7) Other - reported N's or degrees of freedom that were less than what would be
36 expected for the randomized N, but no explanation of the participants included or
37 excluded from the analysis was provided.
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40 (8) Unclear – insufficient information was provided to determine the sample analyzed.

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

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

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50 (1) No dropout – no dropout from treatment and 100% reassessed.
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9 (2) All followed - there were drop-outs from treatment, but all participants, including
10 treatment dropouts, were reassessed.
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12 (3) Statistical ~~imputation or~~ interpolation - used a statistical analysis that ~~imputed or~~
13 interpolated missing data, e.g., mixed-effects model interpolation.
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15 (4) Failure assumed for missing data (missing = failure) - assumed that missing data
16 reflected poor outcome, e.g., relapse.
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18 (5) Baseline assigned - a participant's baseline score was assigned if outcome data were
19 missing.
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21 (6) LOCF - used the imputation strategy of Last Observation Carried Forward.
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23 (7) Censored – last assessment point was used in survival analyses.
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25 (8) Mean - used the mean of the sample followed for missing data.
26
27 (9) Other – used some other imputation of missing data strategy.
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29 (10) Sample followed - conducted analyses with data for the sample of participants that
30 the researchers were able to follow/reassess.
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32 (11) Unclear - no or unclear information provided.
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Statistical Analyses

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

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9 As noted in Table 1, a substantial discrepancy was evident between reporting an ITT
10 strategy versus actually conducting a “true” ITT analysis (i.e., reporting an ITT strategy when
11 something other than ITT was conducted). Of the 165 studies included in this review, 74
12 reported using an ITT strategy. However, less than half of those studies conducted a true ITT
13 analysis ($K=29$; 39%) according to information in study reports. Interestingly, 35% ($K=32$) of the
14 91 studies whose reports made *no* claim of using an ITT strategy, in fact, *did* perform true ITT
15 analyses.
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Table 1.

Reported Using ITT	Conducted True ITT ^a	Sample Analyzed								Total Number of IIT and/or Non-IIT Approaches Used
		Full Random Sample	Full Random Sample (likely)	Random Sample FU	Sufficient Dose	Completer Sample	False Inclusion	Other	Unclear	
No (K=91)	32 (35%)	28 (25%)	4 (4%)	6 (5%)	19 (17%)	31 (28%)	2 (2%)	4 (4%)	16 (14%)	112
Yes (K=74)	29 (39%)	21 (21%)	9 (9%)	7 (7%)	40 (39%)	7 (7%)	8 (8%)	2 (2%)	0 (0%)	102
Total (K=165)	61 (37%)	49 (23%)	13 (6%)	13 (6%)	59 (28%)	38 (18%)	10 (5%)	6 (3%)	16 (8%)	214

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.

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11 Regarding the specific data analytic strategy used, the values in each row of Table 1 do
12 not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45
13 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming
14 failure for dichotomous outcomes AND also used a complete cases approach for continuous
15 outcomes). In such instances, we coded "Reported Using ITT" as "Yes" if the study mentioned
16 using an ITT strategy and coded it as "No" otherwise (i.e., no mention of using an ITT strategy).
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22 The most common approach utilized in studies reporting the use of an ITT strategy, other
23 than use of a true ITT ($K=29$; 39%), involved analyses of data for participants who completed a
24 "sufficient dose" of the medication/treatment ($K=40$; 39%). All other strategies were utilized
25 <10% of the time. The most common analytic method used in studies not mentioning an ITT
26 strategy was actually a true ITT analysis ($K=32$; 29%), followed by analyses of data from
27 completer samples ($K=31$; 28%), analyses for participants who completed a "sufficient dose" of
28 medication/treatment ($K=19$; 17%), and indeterminable strategies (i.e., Unclear; $K=16$; 14%).
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35 Table 2 reports the descriptive information on the missing data strategies employed in the
36 studies using and not using a true ITT approach. Similar to Table 1, the values in each row of
37 Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due
38 to 42 studies utilizing multiple missing data strategies. The most common missing data strategy
39 utilized in studies employing an ITT approach was either unclear ($K=24$; 23%) or involved
40 censoring data at the end of FU procedure in survival analyses ($K=23$; 22%). A study could be
41 categorized as employing an ITT strategy, but having an unclear missing data strategy if, for
42 example, the study reported the full randomized N s from analyses, but it was unclear what
43 particular missing data strategy was utilized. The next most frequently used strategies were
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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.

Conducted True ITT	Missing Data Strategy											Total Number of ITT and/or Non-ITT Approaches Used
	No Tx or FU Dropout	All FU (some tx dropout)	Imputation or Interpolation	Missing = Failure	Baseline Assigned	LOCF	Censored (end of FU) Survival Analysis	Mean Substituted	Other	Sample FU	Unclear	
No (K=104)	0	0	6 (4%)	23 (17%)	1 (1%)	22 (16%)	25 (18%)	3 (2%)	2 (1%)	38 (27%)	17 (12%)	139
Yes (K=61)	1 (1%)	2 (2%)	14 (13%)	14 (13%)	1 (1%)	12 (11%)	23 (22%)	2 (2%)	1 (1%)	11 (10%)	24 (23%)	105
Total (K=165)	1 (>1%)	2 (>1%)	20 (07%)	37 (16%)	2 (>1%)	34 (13%)	48 (19%)	5 (2%)	3 (1%)	49 (19%)	41 (16%)	259 ^a

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).

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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~~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

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9 (0=only end-of treatment assessment, 1= posttreatment and follow-up assessment(s)) was added
10 to the analyses; the results were virtually unchanged.
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Table 3. Change in true ITT analyses over time

	Estimate	SE	t-value	P
(Intercept)	-1.52	0.64	-2.39	0.02*
Year	0.04	0.02	1.85	0.06

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

	Estimate	SE	z-value	P
Fail	0.03	0.02	1.38	0.16
All FU	-0.10	0.09	-1.18	0.24
All FU (some dropout)	-0.09	0.06	-1.43	0.15
Baseline Assigned	0.47	0.36	1.31	0.19
Censored (end of FU)	0.09	0.03	3.19	<0.01*
LOCF	0.06	0.03	2.01	0.045*
Grp Avg	0.07	0.12	0.62	0.54
Mean FU points	0.07	0.07	0.92	0.36
Other	0.05	0.09	0.55	0.59
Sample FU	-0.10	0.02	-4.40	<0.001*
Imputation or Interpolation	0.33	0.09	3.83	<0.001*
Unclear	0.02	0.02	0.94	0.35

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

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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.

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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

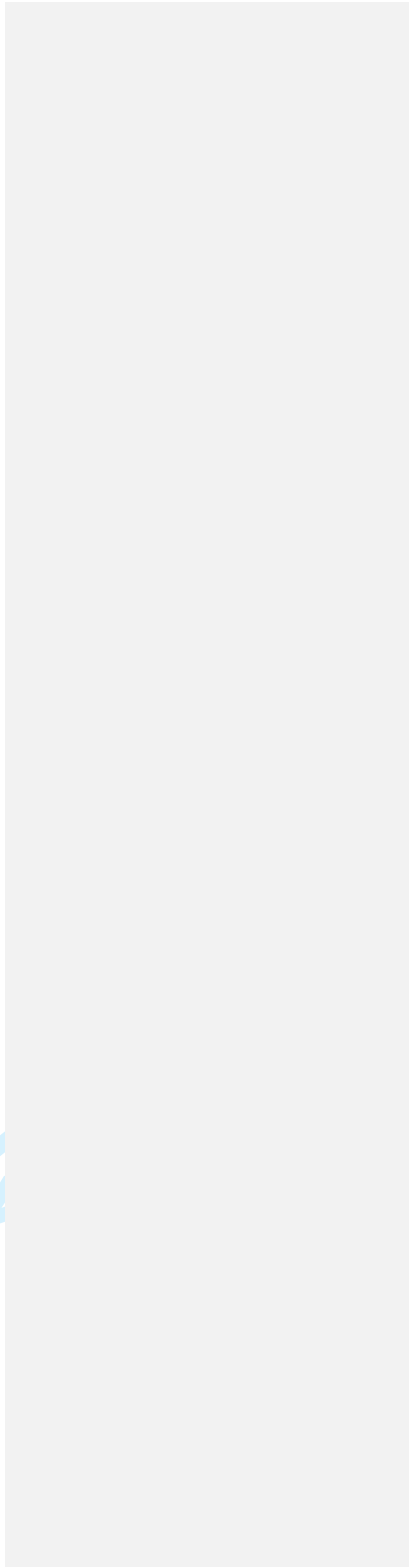
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Ethics

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

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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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