BMJ open

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003464
Article Type:	Research
Date Submitted by the Author:	23-Jun-2013
Complete List of Authors:	Del Re, AC; VA Palo Alto, Maisel, Natalya; VA Palo Alto, Blodgett, Janet; VA Palo Alto, Finney, John; VA Palo Alto Health Care System (152MPD), Center for Health Care Evaluation; Stanford University School of Medicine, Department of Psychiatry & Behavioral Sciences
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Pharmacology and therapeutics, Addiction
Keywords:	STATISTICS & RESEARCH METHODS, CLINICAL PHARMACOLOGY, Substance misuse < PSYCHIATRY

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

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

Research Health Science Specialist, Program Evaluation Resource Center, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, acdelre@gmail.com, 650-493-5000 x2-25842, Fax: 650- 617-2736, A. C. Del Re
Research Health Science Specialist, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, natalya.Maisel@va.gov, 650-493-5000 (press 2 for Menlo Park, ext. 26966), Natalya C. Maisel
Research Associate, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, Janet.Blodgett@va.gov, 650-493-5000 x27292, Janet Blodgett
Research Health Science Specialist, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, john.finney@va.gov, (650) 493-5000 Ext. 2-22848, John W. Finney

Correspondence to: A. C. Del Re acdelre@gmail.com

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

Word count: 2,780, abstract: 326, references: 13, figures: 0, tables: 4

Abstract

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

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

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

Conclusion: Discrepancies in reporting versus actually conducting ITT analyses were found in this body of RCTs. Lack of clarity regarding the missing data strategy used was common.

Consensus on a definition of ITT is important for adequate understanding of research findings. Clearer reporting standards for analyses and the handling of missing data in pharmacotherapy trials and other intervention studies are needed.

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

The intention-to-treat (ITT) analytic strategy is one solution for eliminating or reducing bias in treatment effects arising from missing outcome data in randomized controlled trials (RCTs). [1 2] Although no universally accepted definition of ITT currently exists, the procedure nevertheless is endorsed in the Consolidated Standards for Reporting Trials (CONSORT). [5–7] One particularly succinct definition of a "true ITT" [8] analysis is "once randomized, always analyzed" (Schulz and Grimes, 2002, p. 781). Under this definition, ITT involves analysis of *all* trial participants who were randomized, regardless of adherence to treatment protocol (e.g., dropout/withdrawal or protocol deviations). In other words, defined this way, ITT requires either no attrition or some imputation procedure to account for any missing data.

ITT has several strengths, including (1) helping to preserve the integrity of the randomization process (i.e., groups are expected to be similar except for random variation and

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

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

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

Because both ITT and per protocol approaches to RCT analyses have their strengths, a possible strategy is to conduct an ITT analysis, with a per protocol sensitivity analysis to "bracket" likely effects under different conditions. Nevertheless, ITT analyses are considered the "gold standard" and researchers frequently report the use of this procedure in published literature, even in the absence of a consensual definition. Discrepancies can arise, however, between the type of analyses researchers state in research reports that they conducted and what they *actually* did with respect to use of a "true" ITT analysis or some other procedure based on less than the full randomized sample. For example, in clinical trials in the nursing field, Polit and Gillespie[8] found that for 10.5% of studies, researchers who stated they had used an ITT approach had actually conducted per protocol analyses.

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

Methods

Literature Search

As part of a larger project examining the efficacy of pharmacotherapies for alcohol use disorders and alcohol misuse, [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.

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

Variables

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

(1) Full random sample - analyses involved the total randomized N's (with or without imputation of missing data)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(11) Unclear - no or unclear information provided.

Statistical Analyses

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

Results

As noted in Table 1, a substantial discrepancy was evident between reporting an ITT strategy versus actually conducting a "true" ITT analysis (i.e., reporting an ITT strategy when

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

Table 1.

Reported Using ITT	Conducted True ITT[a]	Sample Analyzed								
		Full Random Sample	Full Random Sample (likely)	Random Sample FU	Sufficient Dose	Completer Sample	False Inclusion	Other	Unclear	**Total Number of IIT and/or Non-ITT Approaches Used**
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: [a]ITT=Full Random Sample or Full Random Sample (likely) categories; *K*=study, column description: (1) Full random sample (analyses involved the total randomized N's), (2) Full random sample (likely) (appears to be using the full randomized sample, but N's are not reported with analyses), (3) Random sample followed-up (attempted to follow-up all randomized participants regardless of amount of medication/treatment completed, and conducted analyses on this sample), (4) Sufficient dose (analyses conducted on only those participants who received a minimum amount of medication/treatment), (5) Completer sample (analyses conducted on only those patients who completed the medication/treatment phase), (6) False inclusion (after randomization, participant is found to not meet inclusion criteria and is subsequently removed from the analyses), (7) Other (analyses report N's or degrees of freedom that are less than what would be expected for the randomized N, but no explanation on the participants included or excluded from the analysis is provided), and (8) Unclear (insufficient information to determine the sample analyzed). Only categories (1) Full random sample and (2) Full random sample (likely) are considered a "true" ITT strategy, whereas the others are considered something other than ITT.

Regarding the specific data analytic strategy used, the values in each row of Table 1 do not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming failure for dichotomous outcomes AND also used a complete cases approach for continuous outcomes). In such instances, we coded "Reported Using ITT" as ”Yes” if the study mentioned using an ITT strategy and coded it as ”No” otherwise (i.e., no mention of using an ITT strategy).

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

Table 2 reports the descriptive information on the missing data strategies employed in the studies using and not using a true ITT approach. Similar to Table 1, the values in each row of Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due to 42 studies utilizing multiple missing data strategies. The most common missing data strategy utilized in studies employing an ITT approach was either unclear (*K*=24; 23%) or involved censoring data at the end of FU procedure in survival analyses (*K*=23; 22%). A study could be categorized as employing an ITT strategy, but having an unclear missing data strategy if, for example, the study reported the full randomized *N*s from analyses, but it was unclear what particular missing data strategy was utilized. The next most frequently used strategies were

assuming missing equals relapse or some other poor outcome ("Failure"; *K*=14; 13%) and using a statistical imputation strategy (*K*=14; 13%), such as a mixed effects model. All other missing data strategies were utilized ≤10% of the time, except the last observation carried forward (LOCF) procedure that was used in (K=12) 11% of the studies.

Table 2.

Conducted True ITT	Missing Data Strategy											
	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	**Total Number of ITT and/or Non-ITT Approaches Used**
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.

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

Table 3. Change in true ITT analyses over time

	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.

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

Conclusion

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

Acknowledgments

Preparation of this manuscript was supported by U.S. National Institute on Alcohol Abuse and Alcoholism Grant No. AA008689 and the U.S. Department of Veterans Affairs, Office of Research and Development, Health Services Research and Development Service and Substance Use Disorder Quality Enhancement Research Initiative. The views expressed are those of the authors and do not necessarily represent the views of the National Institute on Alcohol Abuse and Alcoholism, the Department of Veterans Affairs, or any other U.S. Government entity.

Ethics

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

ICMJE uniform disclosure

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

Contributorship Information

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

Copyright/license for publication

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide license to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) license any third party to do any or all of the above.

1 Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res* 2011;**2**:109–12.

2 Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *Bmj* 1999;**319**:670–4.

3 Little RJ, Rubin DB. *Statistical analysis with missing data*. Wiley New York 1987.

4 Ruiz-Canela M, Martínez-González MA, de Irala-Estévez J. Intention to treat analysis is related to methodological quality. *BMJ* 2000;**320**:1007.

5 Moher D, Schulz K, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *Bmc Med Res Methodol* 2001;**1**:2.

6 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Int J Surg* Published Online First: 2011.http://www.sciencedirect.com/science/article/pii/S1743919111005620 (accessed 6 Mar2013).

7 Zwarenstein M, Treweek S, Gagnier JJ, *et al.* Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* Published Online First: 2008.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3266844/ (accessed 6 Mar2013).

8 Polit DF, Gillespie BM. Intention-to-treat in randomized controlled trials: recommendations for a total trial strategy. *Res Nurs Health* 2010;**33**:355–68.

9 Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. *The Lancet* 2002;**359**:781–5.

10 Avins AL, Pressman A, Ackerson L, *et al.* Placebo Adherence and Its Association with Morbidity and Mortality in the Studies of Left Ventricular Dysfunction. *J Gen Intern Med* 2010;**25**:1275–81.

11 Granger AL, Fehnel SE, Hogue SL, *et al.* An assessment of patient preference and adherence to treatment with Wellbutrin SR: A web-based survey. *J Affect Disord* 2006;**90**:217–21.

12 Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Clin Epidemiol* 2009;**62**:499–505.

13 Maisel NC, Blodgett JC, Wilbourne PL, *et al.* Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? *Addiction* 2013;**108**:275–93.

BMJ Group

BMJ

Licence to BMJ Publishing Group Limited ("BMJ Group") for Publication

To be agreed to by the corresponding author or guarantor on behalf of all authors ("Corresponding Author"). All authors collectively are referred to as the "Contributors"

In consideration of the BMJ Group ("the Publishers") considering to publish the article contained within the original manuscript which includes without limitation any diagrams, photographs, other illustrative material, video, film or any other material howsoever submitted by the Contributor(s) at any time and related to the Contribution ("the Contribution") in the BMJ ("the Journal"), certain rights are required to be granted by each different category of author(s), which are as follows:

1. For employees of the **UK Crown acting in the course of their employment**- a non exclusive Licence, as set out below. All provisions of this document apply. The non exclusivity relates to the original submitted manuscript video, films, images, photographs, diagrams and/or illustrative material only).

2. For employees of the **US Federal Government employees acting in the course of their employment**, no copyright exists and the Contribution is in the public domain so no licence is required to be granted. The Author Warranties below apply (excluding 1.iii).

3. For all other authors, an exclusive Licence, as set out below. All provisions of this document apply.

NB where a Contribution is a multi authored work, each author's element of the Contribution will be dealt with in accordance with 1, 2 or 3 above, as applicable.

The Licence

The Licence granted in accordance with 1 or 3 above is:

A worldwide, licence, to the Publishers and its licensees in perpetuity (subject to the Reversion of Rights set out below), in all forms, formats and media (whether known now or created in the future), **to** i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution and convert or allow conversion into any format including without limitation audio, iii) create any other derivative work(s) based in whole or part on the Contribution, iv) to exploit all subsidiary rights that currently exist or as may exist in the future in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

If you and/or any co-author's employer owns the copyright to your contribution you must obtain in writing the relevant employers' consent to grant the licence and agree to all obligations herein. The author(s) hereby agree that in the event that the BMJ Group sell, the whole or part of its journal business to any third party, the benefit and the burden of the Licence contained herein shall be assigned to that third party.

Additional Rights and Obligations

The author(s) (and their employers as applicable), hereby authorise the Publishers to take such steps as they consider necessary at their own expense in the copyright owners name and on their behalf, if they believe that a third party is infringing or is likely to infringe copyright or the rights granted to the Publishers herein in the Contribution without further recourse to the copyright owner(s).

For Original Research articles and Open Access Funded Articles (as both defined below), the Publishers expressly agree to place the published Contribution for display on PubMed Central (including its international mirror sites) promptly without charge to the authors or their employers (provided Pubmed Central does not charge the Publishers), which will include any Publishers' supplied amendments or retractions**.**

"**Original Research**" means an article reporting a research study, with a research structured abstract and normally appearing in the Research section of the BMJ. "**Open Access Funded Articles**" means articles funded in whole or part by a research grant from a government and/or charitable organisation(s) that requires open access deposit in PubMed Central. Such articles are identified by the reference to a Creative Commons licence.

The author(s) acknowledge and accept that BMJ Group may make additional changes to the contribution as considered necessary in accordance with standard editorial processes whether before or after publication. The Corresponding Author will usually see proofs for their Contribution s and every effort will be made to consult with the Corresponding Author if substantial alterations are made. The BMJ Group may also retract or publish a correction or other notice when it considers this appropriate for legal or editorial reasons and this shall be at its absolute discretion which shall be exercised reasonably.

Reversion of Rights
If the Contribution is not published in either the print or electronic versions of the Journal or any other Publisher(s) products, within 12 months of final acceptance by the BMJ Group, (or as otherwise agreed), any Licence granted herein shall automatically terminate and all rights shall revert to the copyright owner. The Publishers may keep a copy of the Contribution as a record (including via any contractor).

Rights Granted to Owners of the Contribution
Ownership of copyright remains with the author(s) or their employers. All rights not expressly granted are, subject to the Licence terms, reserved by the Publishers. In return for the grant of the Licence herein, the copyright owner(s) shall have the following rights for **non-Commercial Use (unless otherwise stated)** of the Contribution:

1.The right to reproduce a reasonable number (no more than 100) print copies of the final Contribution, by copying or downloading from the BMJ Group website, for personal use and to send copies to colleagues in print or electronic form provided no fee is charged and this is not done on a systematic basis (which includes via mass e-mailings).

2. The right to include the Contribution in a compilation for classroom use (course packs) to be distributed free of charge (other than for direct photocopying cost) to students at the Contributor(s)'s institution or to be stored in digital format in data rooms for access by students as part of their course work and for in house training programmes of the Contributor(s)'s employer or at seminars or conferences subject to a limit of 100 copies per conference or seminar.

3. For all articles (excluding articles commissioned by the Publishers), the right to post a version of the final published version of the Contribution, or any abstract of the final published Contribution on the Contributor(s)'s own and/or his/her institution's website after the Publisher's publication.

4. For all Publisher commissioned articles, the right to post a version of the final published version of the Contribution, or any abstract of the final published Contribution on the Contributor(s)'s own and/or his/her institution's website 12 months after publication.

5. The following statement must accompany the articles posted on the Contributor(s)'s and/or his/her institution's website:

"This article has been published in the BMJ [insert full citation reference] and can also be viewed on the journal's website at www.bmj.com"

6. In addition, for Original Research articles and Open Access Funded Articles copyright owners (and the Publishers) may and may allow third parties to use the Contribution in accordance one of the following Creative Commons licences depending on the source of the research funding as per below:

a) where the Original Research article and/or Open Access Funded Articles **is not** funded by the Wellcome Trust or UK Research Council, the artciles may be re-used under the terms of the Creative Commons Attribution-Non Commercial 3.0 Unported (CC BY-NC 3.0) see:

http://creativecommons.org/licenses/by-nc/3.0/

and

http://creativecommons.org/licenses/by-nc/3.0/legalcode

or any updated versions as determined by the Publisher from time to time.

or

b) where the Original Research article and/or Open Access Funded Articles **is** funded by the Wellcome Trust or UK Research Council, the Contribution may be re-used under the terms of the Creative Commons Attribution 3.0 Unported Licence (CC BY 3.0) see:

http://creativecommons.org/licenses/by/3.0/

and

http://creativecommons.org/licenses/by/3.0/legalcode

or any updated versions as determined by the Publisher from time to time

subject to ensuring the Publishers and the Journal are referenced (including a full citation) as set out above; all third party rights within all images, diagrams, photograph, other illustrative material or films, not owned by the authors or BMJ Group are cleared independently and appropriately; and all the Publishers trademarks are removed from any derivative works and ensuring any translations, for which a prior translation agreement with BMJ Group has not been established, must prominently display the statement: "This is an unofficial translation of an article that appeared in a BMJ Group publication. BMJ Group has not endorsed this translation".

7. The right to publish with the necessary acknowledgement of the Publishers and the Journal, all or part of the material from the published Contribution in a book, essay, position paper, or other non peer reviewed publication authored or edited by the Contributor(s)'s (which may be a Commercial Use). This does not apply to multiple Contributions in the same journal, for which permission from the Publishers must be sought.

8. The right to use selected figures and tables and (of which the author or his employer owns or has licensed) and selected text (up to 300 words) from the Contribution for incorporation within another work published in print or digital format by a third party, so long as full credit is given to the Publishers and use of the parts of the Contribution is non Commercial Use.

9. Subject to it not being contrary to English law to do so (such as for example where the UK has trading or other bans with the country of the Corresponding Authors origin or certain groups of people within), the right to receive a royalty for up to 5 years from publication of 10% of any net receipts less sales commission on single orders in excess of £2000 received by the Publisher for any single Contribution reprint or translation sales to a single third party, subject however to any fee being determined (if charged) at the absolute discretion of the Publishers as may be altered from time to time. If the Publishers receive such an order for reprint sales of the Contribution, they will contact the Corresponding Author at the address given on the published Contribution to find out to whom payment should be made. Corresponding Authors have the responsibility to ensure that all authors have agreed what should be done with any such royalty payment and to keep the Publisher updated with current contact details.

For permission to use materials that are beyond permitted here, visit http://www.bmj.com/about-bmj/resources-readers/permissions

"**Commercial Use"** includes:

- copying or downloading of documents, or linking to such postings, for further redistribution, sale or licensing, for a fee;
- copying, downloading or posting by a site or service that incorporates advertising with such content;
- the inclusion or incorporation of document content in other works or services (other than for legally permitted quotations with an appropriate citation) that is then available for sale or licensing, for a fee.
- use of documents or document content (other than for legally permitted quotations with appropriate citations) by organisations for any promotional or advertising

purposes whether direct or indirect, whether for a fee or otherwise. Distribution by or on behalf of pharmaceutical organisations is considered in all cases as Commercial Use;

- use for the purposes of monetary reward by means of sale, resale, license, loan, hire transfer or other form of commercial exploitation.

Author warranties

1. The author(s) warrant that: i) they are the sole author(s) of the Contribution which is an original work; ii) the whole or a substantial part of the Contribution has not previously been published; iii) they or their employers are the copyright owners of the Contribution; iv) to the best of their knowledge that the Contribution does not contain anything which is libellous, illegal or infringes any third party's copyright or other rights; v) that they have obtained all necessary written consents for any patient information which is supplied with the Contribution and vi) that they have declared or will accurately declare all competing interests to the Publisher.

Anti Bribery

As a service provider to the BMJ Group, you agree that you shall: (a)comply with all applicable laws, statutes, regulations and codes relating to anti-bribery and anti-corruption including but not limited to the Bribery Act 2010 (Relevant Requirements); b) not engage in any activity, practice or conduct which would constitute an offence under sections 1, 2 or 6 of the Bribery Act 2010 (as amended) if such activity, practice or conduct had been carried out in the UK; (c) comply with any Publisher Ethics and Anti-bribery Policy supplied to you from time to time including as contained as follows (Relevant Policies):
http://group.bmj.com/group/about/corporate/Anti-Bribery%20and%20Corruption%20Policy%20-August%202012.pdf;
(d) promptly report to the Chief Executive Officer or Chairman of the Publisher any request or demand for any undue financial or other advantage of any kind received by you in connection with the performance of this Agreement; Breach of this Clause shall be deemed a material breach of this Agreement.

Law and Jurisdiction

To the fullest extent permitted by law, this Agreement will be governed by the laws of England and shall be governed and construed in accordance with the laws of England whose courts shall have exclusive jurisdiction, unless as at the date of formation of this Agreement either i) an English judgement could not be enforced in the Corresponding Author's stated country location; or ii) it would take six months or more for the BMJ Group to enforce an English judgement in the Corresponding Author's stated country location, then it is hereby agreed that this Agreement shall be governed by the laws of the Corresponding Author's stated country (or state if applicable) and their courts shall have jurisdiction. Notwithstanding any of the above, this clause is governed by the laws of England.

The following statement must be included in your manuscript, together with the relevant tick box line below:

"I ***[insert full name***] The Corresponding Author of this article contained within the original manuscript which includes any diagrams & photographs within and any related or stand alone film submitted (the Contribution") has the right to grant on behalf
of all authors and does grant on behalf of all authors, a licence to the BMJ Publishing Group Ltd and its licencees, to permit this Contribution (if accepted) to be published in the BMJ and any other BMJ Group products and to exploit all subsidiary rights, as set out in our licence set out at:
http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse."

IF YOU ARE A NATIONAL INSTITUTE OF HEALTH ("NIH") EMPLOYEE, CONTRACTOR OR TRAINEE the following cover sheet will be accepted by the BMJ Group and NIH and incorporated into the above Licence.

Please tick **one or more** boxes as appropriate:

☐ I am the sole author of the Contribution.

x I am one author signing on behalf of all co-owners of the Contribution.

☐ The Contribution has been made in the course of my employment and I am signing as authorised by my employer.

x I am a US Federal Government employee acting in the course of my employment.
☐ I am not a US Federal Government employee, but some or all of my co-authors are.
☐ I am an employee of the UK Crown* acting in the course of my employment
☐ I am a US Federal Government employee acting in the course of my employment.
☐ I am not a US Federal Government employee, but some or all of my co-authors are.
☐ I am an employee of the UK Crown acting in the course of my employment
☐ I am not an employee of the UK Crown acting in the course of my employment but some/all of my co-authors are.*

*Such authors should consult guidance and if necessary return any completed form.

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

BMJ open

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003464.R1
Article Type:	Research
Date Submitted by the Author:	27-Aug-2013
Complete List of Authors:	Del Re, AC; VA Palo Alto, Maisel, Natalya; VA Palo Alto, Blodgett, Janet; VA Palo Alto, Finney, John; VA Palo Alto Health Care System (152MPD), Center for Health Care Evaluation; Stanford University School of Medicine, Department of Psychiatry & Behavioral Sciences
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Pharmacology and therapeutics, Addiction
Keywords:	STATISTICS & RESEARCH METHODS, CLINICAL PHARMACOLOGY, Substance misuse < PSYCHIATRY

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

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

Research Health Science Specialist, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, aaron.delre@va.gov, 650-493-5000 x2-25842, Fax: 650- 617-2736, A. C. Del Re
Research Health Science Specialist, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, natalya.maisel@va.gov, 650-493-5000 x2-26966, Natalya C. Maisel
Research Associate, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, janet.blodgett@va.gov, 650-493-5000 x2-27292, Janet Blodgett
Research Health Science Specialist, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, john.finney@va.gov, (650) 493-5000 x2-22848, John W. Finney

Correspondence to: A. C. Del Re aaron.delre@va.gov

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

Word count: 3,557, abstract: 298, references: 12, figures: 1, tables: 4

Abstract

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

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

Setting: N/A

Participants: 165 RCTs of pharmacotherapy for alcohol use disorders.

Primary and secondary outcome measures: N/A

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

Conclusions: Discrepancies in reporting versus actually conducting ITT analyses were found in this body of RCTs. Lack of clarity regarding the missing data strategy used was common. Consensus on a definition of ITT is important for adequate understanding of research findings.

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

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

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

ITT has several strengths, including (1) helping to preserve the integrity of the randomization process (i.e., groups are expected to be similar except for random variation and

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

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

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

intervention when used as directed (i.e., efficacy among those who are adherent and able to tolerate the treatment).

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

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

Methods

Literature Search

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

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

Variables

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

(1) Full random sample - analyses involved the total randomized N's (with or without imputation of missing data)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(11) Unclear - no or unclear information provided.

Statistical Analyses

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

Results

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

Table 1.

Reported Using ITT	Conducted True ITT[a]	Sample Analyzed								
		Full Random Sample	Full Random Sample (likely)	Random Sample FU	Sufficient Dose	Completer Sample	False Inclusion	Other	Unclear	**Total Number of IIT and/or Non-ITT Approaches Used**
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: [a]ITT=Full Random Sample or Full Random Sample (likely) categories; *K*=study, column description: (1) Full random sample (analyses involved the total randomized N's), (2) Full random sample (likely) (appears to be using the full randomized sample, but N's are not reported with analyses), (3) Random sample followed-up (attempted to follow-up all randomized participants regardless of amount of medication/treatment completed, and conducted analyses on this sample), (4) Sufficient dose (analyses conducted on only those participants who received a minimum amount of medication/treatment), (5) Completer sample (analyses conducted on only those patients who completed the medication/treatment phase), (6) False inclusion (after randomization, participant is found to not meet inclusion criteria and is subsequently removed from the analyses), (7) Other (analyses report N's or degrees of freedom that are less than what would be expected for the randomized N, but no explanation on the participants included or excluded from the analysis is provided), and (8) Unclear (insufficient information to determine the sample analyzed). Only categories (1) Full random sample and (2) Full random sample (likely) are considered a "true" ITT strategy, whereas the others are considered something other than ITT.

Regarding the specific data analytic strategy used, the values in each row of Table 1 do not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming failure for dichotomous outcomes AND also used a complete cases approach for continuous outcomes). In such instances, we coded "Reported Using ITT" as ”Yes” if the study mentioned using an ITT strategy and coded it as ”No” otherwise (i.e., no mention of using an ITT strategy).

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

Table 2 reports the descriptive information on the missing data strategies employed in the studies using and not using a true ITT approach. Similar to Table 1, the values in each row of Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due to 42 studies utilizing multiple missing data strategies. The most common missing data strategy utilized in studies employing an ITT approach was either unclear (*K*=24; 23%) or involved censoring data at the end of FU procedure in survival analyses (*K*=23; 22%). A study could be categorized as employing an ITT strategy, but having an unclear missing data strategy if, for example, the study reported the full randomized *N*s from analyses, but it was unclear what particular missing data strategy was utilized. The next most frequently used strategies were

assuming missing equals relapse or some other poor outcome ("Failure"; *K*=14; 13%) and using a statistical imputation or interpolation strategy (*K*=14; 13%), such as a mixed effects model. All other missing data strategies were utilized ≤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											
	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	**Total Number of ITT and/or Non-ITT Approaches Used**
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).

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

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

assessment, 1= posttreatment and follow-up assessment(s)) was added to the analyses; the results were virtually unchanged.

Table 3. Change in true ITT analyses over time

	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.

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

Conclusion

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

Acknowledgments

Preparation of this manuscript was supported by U.S. National Institute on Alcohol Abuse and Alcoholism Grant No. AA008689 and the U.S. Department of Veterans Affairs, Office of Research and Development, Health Services Research and Development Service and Substance Use Disorder Quality Enhancement Research Initiative. The views expressed are those of the authors and do not necessarily represent the views of the National Institute on Alcohol Abuse and Alcoholism, the Department of Veterans Affairs, or any other U.S. Government entity.

Ethics

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

ICMJE uniform disclosure

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

Contributorship Information

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

Copyright/license for publication

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide license to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) license any third party to do any or all of the above.

1 Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res* 2011;**2**:109–12. doi:10.4103/2229-3485.83221

2 Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *Bmj* 1999;**319**:670–4.

3 Little RJ, Rubin DB. *Statistical analysis with missing data*. Wiley New York 1987.

4 Ruiz-Canela M, Martínez-González MA, de Irala-Estévez J. Intention to treat analysis is related to methodological quality. *BMJ* 2000;**320**:1007.

5 Moher D, Schulz K, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Med Res Methodol* 2001;**1**:2.

6 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Int J Surg* Published Online First: 2011.http://www.sciencedirect.com/science/article/pii/S1743919111005620 (accessed 6 Mar2013).

7 Zwarenstein M, Treweek S, Gagnier JJ, *et al.* Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* Published Online First: 2008.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3266844/ (accessed 6 Mar2013).

8 Polit DF, Gillespie BM. Intention-to-treat in randomized controlled trials: recommendations for a total trial strategy. *Res Nurs Health* 2010;**33**:355–68.

9 Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. *The Lancet* 2002;**359**:781–5.

10 Avins AL, Pressman A, Ackerson L, *et al.* Placebo Adherence and Its Association with Morbidity and Mortality in the Studies of Left Ventricular Dysfunction. *J Gen Intern Med* 2010;**25**:1275–81. doi:10.1007/s11606-010-1477-8

11 Granger AL, Fehnel SE, Hogue SL, *et al.* An assessment of patient preference and adherence to treatment with Wellbutrin SR: A web-based survey. *J Affect Disord* 2006;**90**:217–21. doi:10.1016/j.jad.2005.08.018

12 Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Clin Epidemiol* 2009;**62**:499–505.

13 Maisel NC, Blodgett JC, Wilbourne PL, *et al.* Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? *Addiction* 2013;**108**:275–93. doi:10.1111/j.1360-0443.2012.04054.x

BMJ Group

BMJ

Licence to BMJ Publishing Group Limited ("BMJ Group") for Publication

To be agreed to by the corresponding author or guarantor on behalf of all authors ("Corresponding Author"). All authors collectively are referred to as the "Contributors"

In consideration of the BMJ Group ("the Publishers") considering to publish the article contained within the original manuscript which includes without limitation any diagrams, photographs, other illustrative material, video, film or any other material howsoever submitted by the Contributor(s) at any time and related to the Contribution ("the Contribution") in the BMJ ("the Journal"), certain rights are required to be granted by each different category of author(s), which are as follows:

1. For employees of the **UK Crown acting in the course of their employment**- a non exclusive Licence, as set out below. All provisions of this document apply. The non exclusivity relates to the original submitted manuscript video, films, images, photographs, diagrams and/or illustrative material only).

2. For employees of the **US Federal Government employees acting in the course of their employment**, no copyright exists and the Contribution is in the public domain so no licence is required to be granted. The Author Warranties below apply (excluding 1.iii).

3. For all other authors, an exclusive Licence, as set out below. All provisions of this document apply.

NB where a Contribution is a multi authored work, each author's element of the Contribution will be dealt with in accordance with 1, 2 or 3 above, as applicable.

The Licence

The Licence granted in accordance with 1 or 3 above is:

A worldwide, licence, to the Publishers and its licensees in perpetuity (subject to the Reversion of Rights set out below), in all forms, formats and media (whether known now or created in the future), **to** i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution and convert or allow conversion into any format including without limitation audio, iii) create any other derivative work(s) based in whole or part on the Contribution, iv) to exploit all subsidiary rights that currently exist or as may exist in the future in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

If you and/or any co-author's employer owns the copyright to your contribution you must obtain in writing the relevant employers' consent to grant the licence and agree to all obligations herein. The author(s) hereby agree that in the event that the BMJ Group sell, the whole or part of its journal business to any third party, the benefit and the burden of the Licence contained herein shall be assigned to that third party.

Additional Rights and Obligations

The author(s) (and their employers as applicable), hereby authorise the Publishers to take such steps as they consider necessary at their own expense in the copyright owners name and on their behalf, if they believe that a third party is infringing or is likely to infringe copyright or the rights granted to the Publishers herein in the Contribution without further recourse to the copyright owner(s).

For Original Research articles and Open Access Funded Articles (as both defined below), the Publishers expressly agree to place the published Contribution for display on PubMed Central (including its international mirror sites) promptly without charge to the authors or their employers (provided Pubmed Central does not charge the Publishers), which will include any Publishers' supplied amendments or retractions**.**

"**Original Research**" means an article reporting a research study, with a research structured abstract and normally appearing in the Research section of the BMJ. "**Open Access Funded Articles**" means articles funded in whole or part by a research grant from a government and/or charitable organisation(s) that requires open access deposit in PubMed Central. Such articles are identified by the reference to a Creative Commons licence.

The author(s) acknowledge and accept that BMJ Group may make additional changes to the contribution as considered necessary in accordance with standard editorial processes whether before or after publication. The Corresponding Author will usually see proofs for their Contribution s and every effort will be made to consult with the Corresponding Author if substantial alterations are made. The BMJ Group may also retract or publish a correction or other notice when it considers this appropriate for legal or editorial reasons and this shall be at its absolute discretion which shall be exercised reasonably.

Reversion of Rights
If the Contribution is not published in either the print or electronic versions of the Journal or any other Publisher(s) products, within 12 months of final acceptance by the BMJ Group, (or as otherwise agreed), any Licence granted herein shall automatically terminate and all rights shall revert to the copyright owner. The Publishers may keep a copy of the Contribution as a record (including via any contractor).

Rights Granted to Owners of the Contribution
Ownership of copyright remains with the author(s) or their employers. All rights not expressly granted are, subject to the Licence terms, reserved by the Publishers. In return for the grant of the Licence herein, the copyright owner(s) shall have the following rights for **non-Commercial Use (unless otherwise stated)** of the Contribution:

1.The right to reproduce a reasonable number (no more than 100) print copies of the final Contribution, by copying or downloading from the BMJ Group website, for personal use and to send copies to colleagues in print or electronic form provided no fee is charged and this is not done on a systematic basis (which includes via mass e-mailings).

2. The right to include the Contribution in a compilation for classroom use (course packs) to be distributed free of charge (other than for direct photocopying cost) to students at the Contributor(s)'s institution or to be stored in digital format in data rooms for access by students as part of their course work and for in house training programmes of the Contributor(s)'s employer or at seminars or conferences subject to a limit of 100 copies per conference or seminar.

3. For all articles (excluding articles commissioned by the Publishers), the right to post a version of the final published version of the Contribution, or any abstract of the final published Contribution on the Contributor(s)'s own and/or his/her institution's website after the Publisher's publication.

4. For all Publisher commissioned articles, the right to post a version of the final published version of the Contribution, or any abstract of the final published Contribution on the Contributor(s)'s own and/or his/her institution's website 12 months after publication.

5. The following statement must accompany the articles posted on the Contributor(s)'s and/or his/her institution's website:

"This article has been published in the BMJ [insert full citation reference] and can also be viewed on the journal's website at www.bmj.com"

6. In addition, for Original Research articles and Open Access Funded Articles copyright owners (and the Publishers) may and may allow third parties to use the Contribution in accordance one of the following Creative Commons licences depending on the source of the research funding as per below:

a) where the Original Research article and/or Open Access Funded Articles **is not** funded by the Wellcome Trust or UK Research Council, the artciles may be re-used under the terms of the Creative Commons Attribution-Non Commercial 3.0 Unported (CC BY-NC 3.0) see:

http://creativecommons.org/licenses/by-nc/3.0/

and

http://creativecommons.org/licenses/by-nc/3.0/legalcode

or any updated versions as determined by the Publisher from time to time.

or

b) where the Original Research article and/or Open Access Funded Articles **is** funded by the Wellcome Trust or UK Research Council, the Contribution may be re-used under the terms of the Creative Commons Attribution 3.0 Unported Licence (CC BY 3.0) see:

http://creativecommons.org/licenses/by/3.0/

and

http://creativecommons.org/licenses/by/3.0/legalcode

or any updated versions as determined by the Publisher from time to time

subject to ensuring the Publishers and the Journal are referenced (including a full citation) as set out above; all third party rights within all images, diagrams, photograph, other illustrative material or films, not owned by the authors or BMJ Group are cleared independently and appropriately; and all the Publishers trademarks are removed from any derivative works and ensuring any translations, for which a prior translation agreement with BMJ Group has not been established, must prominently display the statement: "This is an unofficial translation of an article that appeared in a BMJ Group publication. BMJ Group has not endorsed this translation".

7. The right to publish with the necessary acknowledgement of the Publishers and the Journal, all or part of the material from the published Contribution in a book, essay, position paper, or other non peer reviewed publication authored or edited by the Contributor(s)'s (which may be a Commercial Use). This does not apply to multiple Contributions in the same journal, for which permission from the Publishers must be sought.

8. The right to use selected figures and tables and (of which the author or his employer owns or has licensed) and selected text (up to 300 words) from the Contribution for incorporation within another work published in print or digital format by a third party, so long as full credit is given to the Publishers and use of the parts of the Contribution is non Commercial Use.

9. Subject to it not being contrary to English law to do so (such as for example where the UK has trading or other bans with the country of the Corresponding Authors origin or certain groups of people within), the right to receive a royalty for up to 5 years from publication of 10% of any net receipts less sales commission on single orders in excess of £2000 received by the Publisher for any single Contribution reprint or translation sales to a single third party, subject however to any fee being determined (if charged) at the absolute discretion of the Publishers as may be altered from time to time. If the Publishers receive such an order for reprint sales of the Contribution, they will contact the Corresponding Author at the address given on the published Contribution to find out to whom payment should be made. Corresponding Authors have the responsibility to ensure that all authors have agreed what should be done with any such royalty payment and to keep the Publisher updated with current contact details.

For permission to use materials that are beyond permitted here, visit http://www.bmj.com/about-bmj/resources-readers/permissions

"**Commercial Use"** includes:

- copying or downloading of documents, or linking to such postings, for further redistribution, sale or licensing, for a fee;
- copying, downloading or posting by a site or service that incorporates advertising with such content;
- the inclusion or incorporation of document content in other works or services (other than for legally permitted quotations with an appropriate citation) that is then available for sale or licensing, for a fee.
- use of documents or document content (other than for legally permitted quotations with appropriate citations) by organisations for any promotional or advertising

purposes whether direct or indirect, whether for a fee or otherwise. Distribution by or on behalf of pharmaceutical organisations is considered in all cases as Commercial Use;

- use for the purposes of monetary reward by means of sale, resale, license, loan, hire transfer or other form of commercial exploitation.

Author warranties

1. The author(s) warrant that: i) they are the sole author(s) of the Contribution which is an original work; ii) the whole or a substantial part of the Contribution has not previously been published; iii) they or their employers are the copyright owners of the Contribution; iv) to the best of their knowledge that the Contribution does not contain anything which is libellous, illegal or infringes any third party's copyright or other rights; v) that they have obtained all necessary written consents for any patient information which is supplied with the Contribution and vi) that they have declared or will accurately declare all competing interests to the Publisher.

Anti Bribery

As a service provider to the BMJ Group, you agree that you shall: (a)comply with all applicable laws, statutes, regulations and codes relating to anti-bribery and anti-corruption including but not limited to the Bribery Act 2010 (Relevant Requirements); b) not engage in any activity, practice or conduct which would constitute an offence under sections 1, 2 or 6 of the Bribery Act 2010 (as amended) if such activity, practice or conduct had been carried out in the UK; (c) comply with any Publisher Ethics and Anti-bribery Policy supplied to you from time to time including as contained as follows (Relevant Policies):
http://group.bmj.com/group/about/corporate/Anti-Bribery%20and%20Corruption%20Policy%20-August%202012.pdf;
(d) promptly report to the Chief Executive Officer or Chairman of the Publisher any request or demand for any undue financial or other advantage of any kind received by you in connection with the performance of this Agreement; Breach of this Clause shall be deemed a material breach of this Agreement.

Law and Jurisdiction

To the fullest extent permitted by law, this Agreement will be governed by the laws of England and shall be governed and construed in accordance with the laws of England whose courts shall have exclusive jurisdiction, unless as at the date of formation of this Agreement either i) an English judgement could not be enforced in the Corresponding Author's stated country location; or ii) it would take six months or more for the BMJ Group to enforce an English judgement in the Corresponding Author's stated country location, then it is hereby agreed that this Agreement shall be governed by the laws of the Corresponding Author's stated country (or state if applicable) and their courts shall have jurisdiction. Notwithstanding any of the above, this clause is governed by the laws of England.

The following statement must be included in your manuscript, together with the relevant tick box line below:

"I ***[insert full name***] The Corresponding Author of this article contained within the original manuscript which includes any diagrams & photographs within and any related or stand alone film submitted (the Contribution") has the right to grant on behalf
of all authors and does grant on behalf of all authors, a licence to the BMJ Publishing Group Ltd and its licencees, to permit this Contribution (if accepted) to be published in the BMJ and any other BMJ Group products and to exploit all subsidiary rights, as set out in our licence set out at:
http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse."

IF YOU ARE A NATIONAL INSTITUTE OF HEALTH ("NIH") EMPLOYEE, CONTRACTOR OR TRAINEE the following cover sheet will be accepted by the BMJ Group and NIH and incorporated into the above Licence.

Please tick **one or more** boxes as appropriate:

☐ I am the sole author of the Contribution.

x I am one author signing on behalf of all co-owners of the Contribution.

☐ The Contribution has been made in the course of my employment and I am signing as authorised by my employer.

x I am a US Federal Government employee acting in the course of my employment.
☐ I am not a US Federal Government employee, but some or all of my co-authors are.
☐ I am an employee of the UK Crown* acting in the course of my employment
☐ I am a US Federal Government employee acting in the course of my employment.
☐ I am not a US Federal Government employee, but some or all of my co-authors are.
☐ I am an employee of the UK Crown acting in the course of my employment
☐ I am not an employee of the UK Crown acting in the course of my employment but some/all of my co-authors are.*

*Such authors should consult guidance and if necessary return any completed form.

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

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

Research Health Science Specialist, Center for Health Care~~Program~~ Evaluation ~~Resource Center~~, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, aaron.delre@va.gov~~acdelre@gmail.com~~, 650-493-5000 x2-25842, Fax: 650- 617-2736, A. C. Del Re

Research Health Science Specialist, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, natalya.maisel~~Maisel~~@va.gov, 650-493-5000 x2- ~~(press 2 for Menlo Park, ext.~~ 26966~~),~~ Natalya C. Maisel

Research Associate, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, janet.blodgett~~Janet.Blodgett~~@va.gov, 650-493-5000 x2-27292~~x27292~~, Janet Blodgett

Research Health Science Specialist, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, john.finney@va.gov, (650) 493-5000 x2~~Ext. 2~~-22848, John W. Finney

Correspondence to: A. C. Del Re aaron.delre@va.gov~~acdelre@gmail.com~~

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

Word count: 3,557~~2,780~~, abstract: 298~~326~~, references: 12, figures: 1~~0~~, tables: 4

Formatted: Left, Line spacing: Multiple 1.15 li

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~~.

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

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

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

Field Code Changed
Formatted: Not Superscript/ Subscript
Formatted: Not Superscript/ Subscript
Formatted: Not Superscript/ Subscript
Field Code Changed
Field Code Changed
Formatted: Not Superscript/ Subscript
Field Code Changed
Formatted: Not Superscript/ Subscript
Field Code Changed

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

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

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

Formatted: Not Superscript/ Subscript
Field Code Changed
Field Code Changed
Field Code Changed
Formatted: Not Superscript/ Subscript

the true efficacy of the intervention when used as directed (i.e., efficacy among those who are adherent and able to tolerate the treatment).

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

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

Methods

Literature Search

As part of a larger project examining the efficacy of pharmacotherapies for alcohol use disorders and alcohol misuse, [i.e., 13][12], 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 purused 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:

Field Code Changed

Formatted: Not Superscript/ Subscript

(1) Full random sample - analyses involved the total randomized N's (with or without imputation of missing data)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(11) Unclear - no or unclear information provided.

Statistical Analyses

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

Results

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

Table 1.

Reported Using ITT	Conducted True ITT[a]	Sample Analyzed								
		Full Random Sample	Full Random Sample (likely)	Random Sample FU	Sufficient Dose	Completer Sample	False Inclusion	Other	Unclear	**Total Number of IIT and/or Non-ITT Approaches Used**
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: [a]ITT=Full Random Sample or Full Random Sample (likely) categories; *K*=study, column description: (1) Full random sample (analyses involved the total randomized N's), (2) Full random sample (likely) (appears to be using the full randomized sample, but N's are not reported with analyses), (3) Random sample followed-up (attempted to follow-up all randomized participants regardless of amount of medication/treatment completed, and conducted analyses on this sample), (4) Sufficient dose (analyses conducted on only those participants who received a minimum amount of medication/treatment), (5) Completer sample (analyses conducted on only those patients who completed the medication/treatment phase), (6) False inclusion (after randomization, participant is found to not meet inclusion criteria and is subsequently removed from the analyses), (7) Other (analyses report N's or degrees of freedom that are less than what would be expected for the randomized N, but no explanation on the participants included or excluded from the analysis is provided), and (8) Unclear (insufficient information to determine the sample analyzed). Only categories (1) Full random sample and (2) Full random sample (likely) are considered a "true" ITT strategy, whereas the others are considered something other than ITT.

Regarding the specific data analytic strategy used, the values in each row of Table 1 do not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming failure for dichotomous outcomes AND also used a complete cases approach for continuous outcomes). In such instances, we coded "Reported Using ITT" as ”Yes” if the study mentioned using an ITT strategy and coded it as ”No” otherwise (i.e., no mention of using an ITT strategy).

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

Table 2 reports the descriptive information on the missing data strategies employed in the studies using and not using a true ITT approach. Similar to Table 1, the values in each row of Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due to 42 studies utilizing multiple missing data strategies. The most common missing data strategy utilized in studies employing an ITT approach was either unclear (*K*=24; 23%) or involved censoring data at the end of FU procedure in survival analyses (*K*=23; 22%). A study could be categorized as employing an ITT strategy, but having an unclear missing data strategy if, for example, the study reported the full randomized *N*s from analyses, but it was unclear what particular missing data strategy was utilized. The next most frequently used strategies were

assuming missing equals relapse or some other poor outcome ("Failure"; *K*=14; 13%) and using a statistical imputation or interpolation strategy (*K*=14; 13%), such as a mixed effects model. All other missing data strategies were utilized ≤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											
	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	**Total Number of ITT and/or Non-ITT Approaches Used**
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~~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.~~

Formatted: Font: 9 pt

Formatted Table

The most common missing data method utilized in studies not conducting a true ITT analysis was analyzing the sample followed-up (*K*=38; 27%), followed by censoring at the end of FU procedure (*K*=25; 18%), assuming failure ("Failure"; *K*=23; 17%), last observation carried forward (*K*=23; 16%) and an unclear strategy (*K*=17; 12%). All other missing data strategies were used ≤10% of the time. A study could be categorized as *not* employing an ITT strategy, but still using a missing data strategy of assuming failure or last observation carried forward if, for example, the study assumed failure for missing participants, but something less than the full randomized *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~~changes were~~ 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 ~~However, several~~ statistically significant relationships between missing data strategy and time emerged, as displayed in Table 4. Specifically, censored at end of FU (for survival analyses), last observation carried forward (LOCF), and using a statistical analysis to impute/interpolate missing data (Imputed/Interpolated, e.g., mixed-model interpolation) have become more common over time, whereas analyses conducted on only the samples~~sample~~ of participants that the researchers were able to follow-up (Sample FU) has become less common. To explore whether increasing use of certain missing data strategies over time was confounded with longitudinal methods being increasingly employed, a proxy dummy control variable

(0=only end-of treatment assessment, 1= posttreatment and follow-up assessment(s)) was added to the analyses; the results were virtually unchanged.

Table 3. Change in true ITT analyses over time

	Estimate	SE	t-value	P
(Intercept)	-1.5244	0.6462	-2.3933	0.02*
Year	0.0403	0.02	1.8554	0.0612

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

Formatted Table

Formatted Table

Formatted Table

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.

Field Code Changed

Formatted: Not Superscript/ Subscript

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

Conclusion

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

Acknowledgments

Preparation of this manuscript was supported by U.S. National Institute on Alcohol Abuse and Alcoholism Grant No. AA008689 and the U.S. Department of Veterans Affairs, Office of Research and Development, Health Services Research and Development Service and Substance Use Disorder Quality Enhancement Research Initiative. The views expressed are those of the authors and do not necessarily represent the views of the National Institute on Alcohol Abuse and Alcoholism, the Department of Veterans Affairs, or any other U.S. Government entity.

Ethics

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

ICMJE uniform disclosure

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

Contributorship Information

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

Copyright/license for publication

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide license to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) license any third party to do any or all of the above.

1 Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res* 2011;**2**:109–12. doi:10.4103/2229-3485.83221

2 Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *Bmj* 1999;**319**:670–4.

3 Little RJ, Rubin DB. *Statistical analysis with missing data*. Wiley New York 1987.

4 Ruiz-Canela M, Martínez-González MA, de Irala-Estévez J. Intention to treat analysis is related to methodological quality. *BMJ* 2000;**320**:1007.

5 Moher D, Schulz K, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC~~Bmc~~ Med Res Methodol* 2001;**1**:2.

6 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Int J Surg* Published Online First: 2011.http://www.sciencedirect.com/science/article/pii/S1743919111005620 (accessed 6 Mar2013).

7 Zwarenstein M, Treweek S, Gagnier JJ, *et al.* Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* Published Online First: 2008.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3266844/ (accessed 6 Mar2013).

8 Polit DF, Gillespie BM. Intention-to-treat in randomized controlled trials: recommendations for a total trial strategy. *Res Nurs Health* 2010;**33**:355–68.

9 Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. *The Lancet* 2002;**359**:781–5.

10 Avins AL, Pressman A, Ackerson L, *et al.* Placebo Adherence and Its Association with Morbidity and Mortality in the Studies of Left Ventricular Dysfunction. *J Gen Intern Med* 2010;**25**:1275–81. doi:10.1007/s11606-010-1477-8

11 Granger AL, Fehnel SE, Hogue SL, *et al.* An assessment of patient preference and adherence to treatment with Wellbutrin SR: A web-based survey. *J Affect Disord* 2006;**90**:217–21. doi:10.1016/j.jad.2005.08.018

12 Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Clin Epidemiol* 2009;**62**:499–505.

13~~12~~ Maisel NC, Blodgett JC, Wilbourne PL, *et al.* Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? *Addiction* 2013;**108**:275–93. doi:10.1111/j.1360-0443.2012.04054.x

BMJ open

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003464.R2
Article Type:	Research
Date Submitted by the Author:	27-Sep-2013
Complete List of Authors:	Del Re, AC; VA Palo Alto, Maisel, Natalya; VA Palo Alto, Blodgett, Janet; VA Palo Alto, Finney, John; VA Palo Alto Health Care System (152MPD), Center for Health Care Evaluation; Stanford University School of Medicine, Department of Psychiatry & Behavioral Sciences
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Pharmacology and therapeutics, Addiction
Keywords:	STATISTICS & RESEARCH METHODS, CLINICAL PHARMACOLOGY, Substance misuse < PSYCHIATRY

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

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

Research Health Science Specialist, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, aaron.delre@va.gov, 650-493-5000 x2-25842, Fax: 650- 617-2736, A. C. Del Re
Research Health Science Specialist, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, natalya.maisel@va.gov, 650-493-5000 x2-26966, Natalya C. Maisel
Research Associate, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, janet.blodgett@va.gov, 650-493-5000 x2-27292, Janet Blodgett
Research Health Science Specialist, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, john.finney@va.gov, (650) 493-5000 x2-22848, John W. Finney

Correspondence to: A. C. Del Re aaron.delre@va.gov

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

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

Abstract

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

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

Setting: N/A

Participants: 165 RCTs of pharmacotherapy for alcohol use disorders.

Primary and secondary outcome measures: N/A

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

Conclusions: Discrepancies in reporting versus actually conducting ITT analyses were found in this body of RCTs. Lack of clarity regarding the missing data strategy used was common. Consensus on a definition of ITT is important for adequate understanding of research findings.

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

Strengths and Limitations

Strengths

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

Limitations

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

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

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

ITT has several strengths, including (1) helping to preserve the integrity of the randomization process (i.e., groups are expected to be similar except for random variation and

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

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

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

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

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

Methods

Literature Search

As part of a larger project examining the efficacy of pharmacotherapies for alcohol use disorders and alcohol misuse, [i.e., 13] we identified relevant randomized controlled trials via

several searches of PubMed and PsycINFO conducted at different points over the past decade. Study inclusion criteria were (a) a focus on treating alcohol misuse or an alcohol use disorder; (b) participants 18 years of age or older; (c) publication between 1970 and 2009; (d) a report in the English language; and (e) random assignment of at least five participants each to medication and placebo groups. The details of inclusion/exclusion criteria can be found in Maisel et al.[12]

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

Variables

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

(1) Full random sample - analyses involved the total randomized N's (with or without imputation or interpolation of missing data).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(11) Unclear - no or unclear information provided.

Statistical Analyses

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

Results

As noted in Table 1, a substantial discrepancy was evident between reporting an ITT strategy versus actually conducting a "true" ITT analysis (i.e., reporting an ITT strategy when

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

Table 1.

Reported Using ITT	Conducted True ITT[a]	Sample Analyzed								
		Full Random Sample	Full Random Sample (likely)	Random Sample FU	Sufficient Dose	Completer Sample	False Inclusion	Other	Unclear	**Total Number of IIT and/or Non-ITT Approaches Used**
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: [a]ITT=Full Random Sample or Full Random Sample (likely) categories; *K*=study, column description: (1) Full random sample (analyses involved the total randomized N's), (2) Full random sample (likely) (appears to be using the full randomized sample, but N's are not reported with analyses), (3) Random sample followed-up (attempted to follow-up all randomized participants regardless of amount of medication/treatment completed, and conducted analyses on this sample), (4) Sufficient dose (analyses conducted on only those participants who received a minimum amount of medication/treatment), (5) Completer sample (analyses conducted on only those patients who completed the medication/treatment phase), (6) False inclusion (after randomization, participant is found to not meet inclusion criteria and is subsequently removed from the analyses), (7) Other (analyses report N's or degrees of freedom that are less than what would be expected for the randomized N, but no explanation on the participants included or excluded from the analysis is provided), and (8) Unclear (insufficient information to determine the sample analyzed). Only categories (1) Full random sample and (2) Full random sample (likely) are considered a "true" ITT strategy, whereas the others are considered something other than ITT.

Regarding the specific data analytic strategy used, the values in each row of Table 1 do not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming failure for dichotomous outcomes AND also used a complete cases approach for continuous outcomes). In such instances, we coded "Reported Using ITT" as ”Yes” if the study mentioned using an ITT strategy and coded it as ”No” otherwise (i.e., no mention of using an ITT strategy).

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

Table 2 reports the descriptive information on the missing data strategies employed in the studies using and not using a true ITT approach. Similar to Table 1, the values in each row of Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due to 42 studies utilizing multiple missing data strategies. The most common missing data strategy utilized in studies employing an ITT approach was either unclear (*K*=24; 23%) or involved censoring data at the end of FU procedure in survival analyses (*K*=23; 22%). A study could be categorized as employing an ITT strategy, but having an unclear missing data strategy if, for example, the study reported the full randomized *N*s from analyses, but it was unclear what particular missing data strategy was utilized. The next most frequently used strategies were

assuming missing equals relapse or some other poor outcome ("Failure"; *K*=14; 13%) and using a statistical interpolation strategy (*K*=14; 13%), such as a mixed effects model. All other missing data strategies were utilized ≤10% of the time, except the last observation carried forward (LOCF) procedure that was used in (K=12) 11% of the studies.

Table 2.

Conducted True ITT	Missing Data Strategy											
	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	**Total Number of ITT and/or Non-ITT Approaches Used**
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).

The most common missing data method utilized in studies not conducting a true ITT analysis was analyzing the sample followed-up (*K*=38; 27%), followed by censoring at the end of FU procedure (*K*=25; 18%), assuming failure ("Failure"; *K*=23; 17%), last observation carried forward (*K*=23; 16%) and an unclear strategy (*K*=17; 12%). All other missing data strategies were used ≤10% of the time. A study could be categorized as *not* employing an ITT strategy, but still using a missing data strategy of assuming failure or last observation carried forward if, for example, the study assumed failure for missing participants, but something less than the full randomized *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 interpolate missing data (Interpolation, e.g., mixed effects model interpolation) have become more common over time, whereas analyses conducted on only the samples of participants that the researchers were able to follow-up (Sample FU) has become less common. To explore whether increasing use of certain missing data strategies over time was confounded with longitudinal methods being increasingly employed, a proxy dummy control variable (0=only end-of treatment assessment, 1=

posttreatment and follow-up assessment(s)) was added to the analyses; the results were virtually unchanged.

Table 3. Change in true ITT analyses over time

	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.

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

Preparation of this manuscript was supported by U.S. National Institute on Alcohol Abuse and Alcoholism Grant No. AA008689 and the U.S. Department of Veterans Affairs, Office of Research and Development, Health Services Research and Development Service and Substance Use Disorder Quality Enhancement Research Initiative. The views expressed are those of the authors and do not necessarily represent the views of the National Institute on Alcohol Abuse and Alcoholism, the Department of Veterans Affairs, or any other U.S. Government entity.

Ethics

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

Funding

U.S. National Institute on Alcohol Abuse 3 and Alcoholism Grant No. AA008689 and the U.S. Department of Veterans Affairs, Office of Research and Development, Health Services Research and Development Service and Substance Use Disorder Quality Enhancement Research Initiative funded this research.

Competing interest

There are no competing interests.

Data sharing

No additional data available.

ICMJE uniform disclosure

All authors have completed the ICMJE uniform disclosure form at 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.

Copyright/license for publication

1 Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res* 2011;**2**:109–12. doi:10.4103/2229-3485.83221

2 Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *Bmj* 1999;**319**:670–4.

3 Little RJ, Rubin DB. *Statistical analysis with missing data*. Wiley New York 1987.

4 Ruiz-Canela M, Martínez-González MA, de Irala-Estévez J. Intention to treat analysis is related to methodological quality. *BMJ* 2000;**320**:1007.

5 Moher D, Schulz K, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Med Res Methodol* 2001;**1**:2.

6 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Int J Surg* Published Online First: 2011.http://www.sciencedirect.com/science/article/pii/S1743919111005620 (accessed 6 Mar2013).

7 Zwarenstein M, Treweek S, Gagnier JJ, *et al.* Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* Published Online First: 2008.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3266844/ (accessed 6 Mar2013).

8 Polit DF, Gillespie BM. Intention-to-treat in randomized controlled trials: recommendations for a total trial strategy. *Res Nurs Health* 2010;**33**:355–68.

9 Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. *The Lancet* 2002;**359**:781–5.

10 Avins AL, Pressman A, Ackerson L, *et al.* Placebo Adherence and Its Association with Morbidity and Mortality in the Studies of Left Ventricular Dysfunction. *J Gen Intern Med* 2010;**25**:1275–81. doi:10.1007/s11606-010-1477-8

11 Granger AL, Fehnel SE, Hogue SL, *et al.* An assessment of patient preference and adherence to treatment with Wellbutrin SR: A web-based survey. *J Affect Disord* 2006;**90**:217–21. doi:10.1016/j.jad.2005.08.018

12 Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Clin Epidemiol* 2009;**62**:499–505.

13 Maisel NC, Blodgett JC, Wilbourne PL, *et al.* Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? *Addiction* 2013;**108**:275–93. doi:10.1111/j.1360-0443.2012.04054.x

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

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

Research Health Science Specialist, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, aaron.delre@va.gov, 650-493-5000 x2-25842, Fax: 650- 617-2736, A. C. Del Re
Research Health Science Specialist, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, natalya.maisel@va.gov, 650-493-5000 x2-26966, Natalya C. Maisel
Research Associate, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, janet.blodgett@va.gov, 650-493-5000 x2-27292, Janet Blodgett
Research Health Science Specialist, Center for Health Care Evaluation, VA Palo Alto Health Care System (152MPD), 795 Willow Rd, Menlo Park, CA 94025, john.finney@va.gov, (650) 493-5000 x2-22848, John W. Finney

Correspondence to: A. C. Del Re aaron.delre@va.gov

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

Word count: 3,557, abstract: 298, references: 12, figures: 1, tables: 4

Abstract

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

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

Strengths

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

Limitations

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

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

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

ITT has several strengths, including (1) helping to preserve the integrity of the randomization process (i.e., groups are expected to be similar except for random variation and

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

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

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

intervention when used as directed (i.e., efficacy among those who are adherent and able to tolerate the treatment).

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

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

Methods

Literature Search

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

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

Variables

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

(1) Full random sample - analyses involved the total randomized N's (with or without imputation or interpolation of missing data~~)~~).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(11) Unclear - no or unclear information provided.

Statistical Analyses

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

Results

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

Table 1.

Reported Using ITT	Conducted True ITT[a]	Sample Analyzed								
		Full Random Sample	Full Random Sample (likely)	Random Sample FU	Sufficient Dose	Completer Sample	False Inclusion	Other	Unclear	**Total Number of IIT and/or Non-ITT Approaches Used**
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: [a]ITT=Full Random Sample or Full Random Sample (likely) categories; *K*=study, column description: (1) Full random sample (analyses involved the total randomized N's), (2) Full random sample (likely) (appears to be using the full randomized sample, but N's are not reported with analyses), (3) Random sample followed-up (attempted to follow-up all randomized participants regardless of amount of medication/treatment completed, and conducted analyses on this sample), (4) Sufficient dose (analyses conducted on only those participants who received a minimum amount of medication/treatment), (5) Completer sample (analyses conducted on only those patients who completed the medication/treatment phase), (6) False inclusion (after randomization, participant is found to not meet inclusion criteria and is subsequently removed from the analyses), (7) Other (analyses report N's or degrees of freedom that are less than what would be expected for the randomized N, but no explanation on the participants included or excluded from the analysis is provided), and (8) Unclear (insufficient information to determine the sample analyzed). Only categories (1) Full random sample and (2) Full random sample (likely) are considered a "true" ITT strategy, whereas the others are considered something other than ITT.

Regarding the specific data analytic strategy used, the values in each row of Table 1 do not sum to the total number of studies in the first column (i.e., "Reported Using ITT") due to 45 studies utilizing both ITT and non-ITT analyses (e.g., conducted an ITT analysis assuming failure for dichotomous outcomes AND also used a complete cases approach for continuous outcomes). In such instances, we coded "Reported Using ITT" as "Yes" if the study mentioned using an ITT strategy and coded it as "No" otherwise (i.e., no mention of using an ITT strategy).

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

Table 2 reports the descriptive information on the missing data strategies employed in the studies using and not using a true ITT approach. Similar to Table 1, the values in each row of Table 2 do not sum to the total number of studies in the first column (i.e., "Conducted ITT") due to 42 studies utilizing multiple missing data strategies. The most common missing data strategy utilized in studies employing an ITT approach was either unclear (*K*=24; 23%) or involved censoring data at the end of FU procedure in survival analyses (*K*=23; 22%). A study could be categorized as employing an ITT strategy, but having an unclear missing data strategy if, for example, the study reported the full randomized *N*s from analyses, but it was unclear what particular missing data strategy was utilized. The next most frequently used strategies were

assuming missing equals relapse or some other poor outcome ("Failure"; *K*=14; 13%) and using a statistical ~~imputation or~~ interpolation strategy (*K*=14; 13%), such as a mixed effects model. All other missing data strategies were utilized ≤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											
	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	**Total Number of ITT and/or Non-ITT Approaches Used**
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).

The most common missing data method utilized in studies not conducting a true ITT analysis was analyzing the sample followed-up (*K*=38; 27%), followed by censoring at the end of FU procedure (*K*=25; 18%), assuming failure ("Failure"; *K*=23; 17%), last observation carried forward (*K*=23; 16%) and an unclear strategy (*K*=17; 12%). All other missing data strategies were used ≤10% of the time. A study could be categorized as *not* employing an ITT strategy, but still using a missing data strategy of assuming failure or last observation carried forward if, for example, the study assumed failure for missing participants, but something less than the full randomized *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

(0=only end-of treatment assessment, 1= posttreatment and follow-up assessment(s)) was added to the analyses; the results were virtually unchanged.

Table 3. Change in true ITT analyses over time

	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

Formatted Table

Formatted Table

Discussion

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

Among the studies conducting a true ITT strategy, it was unclear what missing data strategy was used in nearly 25% of these studies. Lack of clarity in journal articles about how missing data were handled makes it difficult for readers to critically assess the study findings. A per protocol analysis answers questions of an explanatory nature, e.g., "how efficacious is this treatment for those adherent to the treatment?" In contrast, an ITT analysis provides more realistic (and usually less biased) estimates of the average treatment effects in the "real-world," as it accounts for both patient dropout and non-adherence to treatment. If findings from a per protocol analysis are incorrectly perceived as coming from an ITT analysis, treatment effects under more routine conditions of care will be overestimated. Journal editors and peer reviewers should be attentive to these issues and request that authors provide a clear description of the sample analyzed (i.e., ITT, modified ITT, per protocol) in their studies, along with details regarding how missing data were handled.

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

Conclusion

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

Acknowledgments

Preparation of this manuscript was supported by U.S. National Institute on Alcohol Abuse and Alcoholism Grant No. AA008689 and the U.S. Department of Veterans Affairs, Office of Research and Development, Health Services Research and Development Service and Substance Use Disorder Quality Enhancement Research Initiative. The views expressed are those of the authors and do not necessarily represent the views of the National Institute on Alcohol Abuse and Alcoholism, the Department of Veterans Affairs, or any other U.S. Government entity.

Ethics

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

ICMJE uniform disclosure

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

Contributorship Information

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

Copyright/license for publication

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide license to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) license any third party to do any or all of the above.

1 Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res* 2011;**2**:109–12. doi:10.4103/2229-3485.83221

2 Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *Bmj* 1999;**319**:670–4.

3 Little RJ, Rubin DB. *Statistical analysis with missing data*. Wiley New York 1987.

4 Ruiz-Canela M, Martínez-González MA, de Irala-Estévez J. Intention to treat analysis is related to methodological quality. *BMJ* 2000;**320**:1007.

5 Moher D, Schulz K, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Med Res Methodol* 2001;**1**:2.

6 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Int J Surg* Published Online First: 2011.http://www.sciencedirect.com/science/article/pii/S1743919111005620 (accessed 6 Mar2013).

7 Zwarenstein M, Treweek S, Gagnier JJ, *et al.* Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* Published Online First: 2008.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3266844/ (accessed 6 Mar2013).

8 Polit DF, Gillespie BM. Intention-to-treat in randomized controlled trials: recommendations for a total trial strategy. *Res Nurs Health* 2010;**33**:355–68.

9 Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. *The Lancet* 2002;**359**:781–5.

10 Avins AL, Pressman A, Ackerson L, *et al.* Placebo Adherence and Its Association with Morbidity and Mortality in the Studies of Left Ventricular Dysfunction. *J Gen Intern Med* 2010;**25**:1275–81. doi:10.1007/s11606-010-1477-8

11 Granger AL, Fehnel SE, Hogue SL, *et al.* An assessment of patient preference and adherence to treatment with Wellbutrin SR: A web-based survey. *J Affect Disord* 2006;**90**:217–21. doi:10.1016/j.jad.2005.08.018

12 Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Clin Epidemiol* 2009;**62**:499–505.

13 Maisel NC, Blodgett JC, Wilbourne PL, *et al.* Meta-analysis of naltrexone and acamprosate for treating alcohol use disorders: when are these medications most helpful? *Addiction* 2013;**108**:275–93. doi:10.1111/j.1360-0443.2012.04054.x