A comparison between phase-III trials and a phase-IV study of nalmefene in alcohol use disorder patients. Is there a difference?

Una comparación entre los estudios de fase 3 y un estudio de fase 4 de nalmefeno en el trastorno por uso de alcohol. ¿Existen diferencias?

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Abstract

Concerns regarding the external validity of phase-III trials are common to many medical disciplines, with relevant discrepancies found between experimental and clinical samples in some diseases such as hypertension. The aim of this study was to compare the samples included in the pivotal, phase-III clinical trials of nalmefene with that of a recently conducted phase-IV trial. Baseline characteristics of the studies were compared through univariate analysis. Significant differences were found in the percentage of low-risk drinkers included. Differences were also found in the prescription and intake pattern of nalmefene, as well as in the rate of psychiatric and addictive comorbidities, which were much higher in the phase-IV study. These data suggest that in the field of alcohol use disorders there are also relevant differences between experimental and clinical samples, a fact that reinforces the need for phase-III trials to be balanced with observational, phase-IV trials.

Keywords: Phase-III trial; Phase-IV trial; External validity; Nalmefene; Alcohol use disorders.

Resumen

En muchas disciplinas médicas existen diferencias significativas entre las muestras procedentes de estudios experimentales y las muestras procedentes de ámbitos clínicos, como es por ejemplo el caso de la hipertensión. El objetivo del presente estudio fue comparar las muestras procedentes de los ensayos pivotales de fase 3 de nalmefeno con la muestra de un estudio de fase 4 realizado recientemente. Las características basales de las muestras se compararon mediante técnicas univariantes. Se encontraron diferencias significativas entre el porcentaje de los participantes consumidores de alcohol de bajo riesgo. También se encontraron diferencias en los patrones de prescripción y en la toma de nalmefeno, así como en el porcentaje de comorbilidades psiquiátricas y adictivas, que fueron muy superiores en el estudio de fase 4. En su conjunto, estos datos sugieren que en el campo del trastorno por uso de alcohol (TUA) existen también diferencias relevantes entre muestras procedentes de estudios experimentales y muestras procedentes de estudios clínico-observacionales. Este hecho refuerza la necesidad de que los estudios de fase 3 sean complementados con estudios observacionales de fase 4.

Palabras clave: Fase 3; Fase 4; Validez externa; Nalmefeno; Trastorno por uso de alcohol.

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Alcohol imposes a heavy burden on societies around the world, most of which is inflicted by those who drink heavily, that is, those affected by an alcohol use disorder (Whiteford et al., 2013). The treatment of AUDs is therefore of high importance. A combination of psychosocial and pharmacological strategies is usually recommended. Regarding pharmacological treatment, last decades have witnessed the appearance of different compounds with proven efficacy on several outcomes. Such is the case of nalmefene, an opiod antagonist recently approved for the treatment of alcohol patients who aim for a reduction objective. The approval was based on three pivotal phase-III trials (Gual et al., 2013; Mann, Bladström, Torup, Gual & van den Brink, 2013; van den Brink et al., 2013).

Phae-III trials are a basic and very important step in the process leading to drug approval by regulatory agencies. They are usually largely sized, randomized trials with a homogenous study sample. All these characteristics lead to high statistical power and high internal validity.

While experimental designs such as those of phase-III studies are essential for internal validity assessment and are the cornerstone of drug efficacy assessment, it has been extensively noted in many areas that, usually, external validity remains disproportionally neglected (Dekkers, von Elm, Algra, Romijn & Vandenbroucke, 2010; Pearson & Coomber, 2010; Rothwell, 2005). This fact might yield relevant consequences, such as the fact that patients from experimental settings might differ significantly from patients in real world settings (Hoertel et al., 2014; Uijen, Bakx, Mokkink & van Weel, 2007), ultimately jeopardizing the feasibility, applicability and even the relevance of experimental findings(Persaud & Mamdani, 2006).

In this context, previous studies in several diseases such as hypertension, social anxiety rheumatoid arthritis and others(Farahani, Levine, Gaebel & Thabane, 2005), have found that phase-III and phase-IV patients are not always similar, a fact that could have relevant implications. Therefore, we believe it is also necessary to evaluate, in the field of alcohol use disorders, whether patients in "real-life" are comparable to patients of previous experimental studies, and what differences might exist. This is in fact, one of the reasons leading to the need of phase-IV studies (Linden, 1984).

In the present paper we aim at comparing the baseline characteristics of patients recently enrolled in a phase-IV trial of nalmefene with those of patients who participated in the phase-III trials.

Method

The present study compared patients from two different types of studies. The first group of patients belongs to an observational, multisite, single arm, phase 4 study conducted among alcohol dependent outpatients taking nalmefene for the first time as a treatment for alcohol use disorder. To be enrolled in this phase-IV trial, patients had to be adults (≥18 years) diagnosed with alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR) or the International Classification of Diseases (ICD-10) criteria who according to routine clinical criteria, had been started on nalmefene for the first time. The study consisted of 4 visits: baseline, 1 month, 6 months and 12 months. Patients continued to receive their usual treatment independent of study visits and procedures.

The second group consisted of patients who participated in the three phase-III trials of nalmefene. Data from these patients was gathered from existing publications in the literature. Phase-III trials were kept independent of each other for study comparisons. Therefore, a total of 4 groups were formed. Each phase-III trial was compared to the phase-IV study. All available variables for the 4 studies at baseline were included. Statistical comparisons were conducted with univariate tests (T-test or chi-square depending on variable type).

Results

A total of 110 patients were included from 4 sites in the Spanish region of Catalonia, between 2015 and 2016. A full description of the phase-IV study results is available elsewhere (Barrio, Ortega, Guardia, Roncero, Yuguero & Gual, 2018) . Table 1 illustrates the differences between this study and the phase III trials of nalmefene regarding the main study variables at baseline.

Important differences were found regarding the percentage of low drinking risk level, with the present study showing a much higher rate (45%) as compared to the ESENSE trials (1-5%). Consequently, in the high/very high categories, numbers were reversed, with 38% of patients in this study allocated to this category, as compared to 76-78% in the phase III trials. Another illustration of these relevant differences is the fact that in this study, mean alcohol consumption (60.4 g/day) was significantly lower (85-92 g/day in ESENSE trials).

Also relevant, we found a significantly lower prevalence of family history of alcohol problems in our sample. Finally, when comparing the percentage of days with study medication intake, a higher proportion in the phase-IV trial was observed. Also relevant is the fact that the number of patients taking nalmefene on a daily basis was higher. Given the inclusion criteria of phase-III tirals, addictive comorbidities were only present in the phase-IV study. Similarly, only the SENSE trial allowed psychiatric comorbidities among patients, which were nonetheless much less frequent than in the phase-IV trial.

Discussion

This study found significant differences between phase-IV and phase-III patients taking nalmefene. When compared to phase-III trials, patients in real settings showed a higher rate of both addictive and psychiatric comorbidities, a fact that is in sharp contrast with the samples of randomized, controlled studies, which are usually more restrictive in their inclusion criteria. In fact, the high rate of psychiatric comorbidities in alcohol patients is a well documented phenomenon (Fein, 2015; Flensborg-Madsen et al., 2009). This finding supports the criticisms targeted at the external validity of experimental studies (Persaud & Mamdani, 2006) and at the same time suggests that, studies like the SENSE trial (van den Brink et al., 2014), where patients with psychiatric comorbidities were included, should be the norm rather than the exception.

It should also be noted that a great number of patients in the phase-IV trial were already labeled as low-risk drinkers at baseline. In fact, almost half of the patients were considered low-risk drinkers at study entry, a fact that at first sight could seem contradictory to nalmefene therapeutic indications. It should be noted, however, that risk assessment for phase-IV study purposes was based on the previous 28 days. It is probable that clinicians, when deciding the risk category of patients, take into account a longer timeframe. Also, similar to what has been observed in phase-III trials, it is possible that the mere fact of patients deciding to enter into treatment leads to significant reductions in drinking. Interestingly, the percentage of low risk drinkers in the phase-IV trial is very similar to that of phase-III trials if we add up the baseline low risk drinkers and the low risk drinkers prior to nalmefene initiation.

Age at onset of drinking problems was another variable showing clear differences. While real differences could be expected between real practice and experimental studies, it could also be due to different methods of recollection. While a younger age of onset of drinking problems could suggest a greater disease severity, baseline alcohol parameters were, conversely, milder in the phase-IV study sample, with lesser heavy drinking days and lesser mean alcohol consumption. It also looks like patients in the phase-IV trial had a superior rate of medication intake. In fact, results of the phase-IV (Barrio et al., 2018) suggest that, despite being labeled as an "as-needed" medication, patients and clinicians in real world practice will frequently use it on a scheduled, daily basis.

Several limitations apply to this study. The most relevant is the different design of phase-IV and phase-III trials, a fact

Table 1. Main sociodemographic characteristics of included patients and comparison with phase III trials

Characteristic	Phase IV (n=110)	ESENSE 1 (n=306)	ESENSE 2 (n= 358)	SENSE (n=509)
Age: mean (SD)	44.4 (9.4)	51.0 (10.1)*	45.1 (10.7]	44.3 (11.2]
Sex male (%)	66.4%	66.6%	74.3%	77.2%*
Higher education (%)	27.3%			32.4%
Age at the Onset of Drinking Problems: mean (SD)	23 (12.4)	37.9 (13.1)*	32.6 (10.8)*	33.4 (11.6)*
Drinking Risk Level				
Low (%)	45.5%	3%*	1.4%*	15.5%*
Medium (%)	16.4%	22.2%	19.0%	32.8%*
High (%)	21.8%	37.3%*	36.0%*	29.1%
Very High (%)	16.3%	39.9%*	43.6%*	22.4%
g-Glutamyltransferase (IU/L) : mean (SD)	84 (128.2)	51.7	51.8	40.9
Alanine Aminotransferase (IU/L) : mean (SD)	29.2 (15.5)	29.2	28.7	28.5
Previously Treated for Alcohol Dependence (%)	46.4%	29.7%*	39.7%	33.6%*
Previously Treated for Alcohol Withdrawal (%)	30%	19.6%*	15.9%*	26.9%
Personal history of psychiatric problems (%)	36.4%			3.7%*
Family History of Alcohol Problems (%)	48.2%	62.4%*	60.1%*	51.7%
Addictive comorbidities*** (past or present) (%)	65.5%			
Percentage of days taking study medication (%)	64%	48%*	57%	48.4%*
Monthly heavy drinking days (baseline) : mean (SD)	13.5 (11)	19.5 (7.3)*	19.7 (7.0)*	14.1 (6.2)
Mean alcohol consumption (grams per day; baseline) : mean (SD)	60.4 (74.6)	84.8 (42.1)*	92.2 (46.9)*	68.6 (40.0)

Note. *=significant at p<0.05 when compared to phase IV study values with univariate tests (t-student or chi-square).
** defined as the presence of diabetes, hypertension, high blood cholesterol or any other significant medical condition.
*** defined as any substance use disorder (except nicotine dependence), past or current, as clinically evaluated in the first visit of the study.

that implies caution when interpreting the comparisons undertaken in this study. Also, it is important to mention that the phase-IV trial included patients from 4 different sites, all belonging to the same city. In this sense, phase-III trials had a much wider representation, with patients from different countries being included.

Conclusion

All in all we believe this study suggests that, as previously shown in other diseases, samples from experimental studies might differ in some aspects from patients in routine clinical practice. While efforts targeted at increasing phase-III trials' external validity should be encouraged, this study also confirms that phase-IV studies are indeed a crucial part of the research process.

Contributions

Pablo Barrio and Antoni Gual designed the study. Pablo Barrio wrote the first draft of the manuscript. All other authors contributed to the editing and final review of the manuscript. All authors approved the final paper.

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Conflict of interest

Dr. Barrio, Dr. Roncero, Dr. Guardia and Dr. Gual have received honoraria from Lundbeck. Dr. Barrio has also received honoraria from Pfizer. Dr. Roncero has also received honoraria from Janssen-Cilag, Otsuka, Server, GSK, Rovi, Astra, MSD and Sanofi. Dr. Yuguero and Dr. Ortega have no conflict of interest to declare

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